Research in Progress: FY 1992

**Summaries of Projects Sponsored by the
Office of Health and Environmental Research**

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MASTER

Contents

Table of Contents	v
Legislative History	xi
Foreword	xiii
Introduction	xv
Research in Progress: Overview	xxv
Research Profiles of Major OHER-Supported Programs at DOE Facilities	xxxv
Multiprogram Laboratories	xxxv
Special Purpose Laboratories	xlix
Abbreviations and Acronyms	iv

Table of Contents

Summaries of FY 1992 Research

Health Research

Radiation and Chemical Effects:

Biological Effects Studies 1

Intramural DOE Laboratories

Argonne National Laboratory	1
Brookhaven National Laboratory	5
University of California, San Francisco	5
Inhalation Toxicology Research Institute	6
Lawrence Berkeley Laboratory	11
Lawrence Livermore National Laboratory	14
Los Alamos National Laboratory	15
Oak Ridge Institute for Science and Education	16
Oak Ridge National Laboratory	17
Pacific Northwest Laboratory	20

Offsite Grants

Brandeis University	24
University of California, Davis	24
University of California, Los Angeles Laboratory of Biomedical and Environmental Sciences	25
University of California, San Diego	25
University of California, San Diego School of Medicine	25
Case Western Reserve University	26
Columbia University College of Physicians and Surgeons	26
Duke University Medical Center	26
Fred Hutchinson Cancer Research Center	27
The Johns Hopkins University School of Hygiene and Public Health	27
University of Michigan	27
University of New Mexico School of Medicine	28
New York University Medical Center	29
Oakland University	29
Sloan Kettering Memorial Cancer Center	30
University of Southern California	30
SRI International	30
St. Mary's Hospital and Medical Center	31
University of Texas, Medical Branch at Galveston	31
University of Vermont	31
University of Vermont College of Medicine	32

Wake Forest University Bowman Gray

School of Medicine 32

University of Wisconsin Clinical Cancer Center 32

Radiation and Chemical Effects:

Cellular and Molecular Biology 33

Intramural DOE Laboratories

Argonne National Laboratory	33
Brookhaven National Laboratory	33
University of California, San Francisco	35
Lawrence Berkeley Laboratory	37
Lawrence Livermore National Laboratory	38
Los Alamos National Laboratory	40
Oak Ridge Institute for Science and Education	43
Oak Ridge National Laboratory	43

Offsite Grants

Associated Western Universities	46
University of California, Berkeley	46
University of California, Davis	47
University of California, Irvine	47
University of California, Los Angeles Laboratory of Biomedical and Environmental Sciences	48
University of California, Los Angeles School of Medicine	49
University of California, San Diego	49
University of Chicago	49
University of Chicago Medical Center	49
The Johns Hopkins University	50
The Johns Hopkins University School of Hygiene and Public Health	50
Louisiana State University	51
Massachusetts Institute of Technology	51
Michigan State University College of Osteopathic Medicine	52
National Institute of Standards and Technology	52
New York University	52
University of Rochester School of Medicine	53
University of South Carolina	54
University of Washington	54

Radiation and Chemical Effects: Physical and Chemical Processes 54

Intramural DOE Laboratories

Argonne National Laboratory	54
Lawrence Berkeley Laboratory	55
Los Alamos National Laboratory	55
Oak Ridge National Laboratory	56
Pacific Northwest Laboratory	58

Offsite Grants

Case Western Reserve University	59
Columbia University	59
Florida State University	60
Louisiana State University	60
Mount Sinai School of Medicine	61
National Institute of Standards and Technology	61
University of Nebraska	62
New York University	62
Pennsylvania State University	62
University of Rochester	63

Radiation and Chemical Effects: Instrumentation Research 63

Intramural DOE Laboratories

Ames Laboratory	63
Argonne National Laboratory	63
Brookhaven National Laboratory	64
Environmental Measurements Laboratory	64
Idaho National Engineering Laboratory	66
Inhalation Toxicology Research Institute	67
Lawrence Berkeley Laboratory	67
Lawrence Livermore National Laboratory	68
Oak Ridge National Laboratory	68
Pacific Northwest Laboratory	70

Offsite Grants

The Aerospace Corporation	72
California Institute of Technology	72
Clarkson University	73
Columbia University	73
Comstock, Inc.	73
Farachem Technology, Inc.	74
Indiana University	74
University of Michigan	74
National Council on Radiation Protection and Measurements	74
National Institute of Standards and Technology	75
Northeastern University	75
Pennsylvania State University	76
Physical Sciences, Inc.	76
Princeton University, School of Engineering and Applied Science	77
University of Southern California	77

Southwest Sciences, Inc.	78
Spectral Sciences, Inc.	78
University of Wisconsin	79

Biotechnology: Human Genome 79

Intramural DOE Laboratories

Ames Laboratory	79
Argonne National Laboratory	80
Brookhaven National Laboratory	80
Lawrence Berkeley Laboratory	82
Lawrence Livermore National Laboratory	87
Los Alamos National Laboratory	91
Oak Ridge Institute for Science and Engineering	98
Oak Ridge National Laboratory	98
Pacific Northwest Laboratory	102

Offsite Grants

Adelaide Children's Hospital	102
Advanced Technology Applications, Inc.	103
Affymax Research Institute	103
University of Alberta	103
American Type Culture Collection	104
University of Arizona	104
Arizona State University	105
Atom Sciences, Inc.	105
Baylor College of Medicine	105
Beckman Research Institute, City of Hope	107
BIODE, Inc.	107
Boston University	108
University of California, Berkeley	108
University of California, Cedars—Sinai Medical Center	109
University of California, San Francisco	109
California Institute for Biological Research	110
California Institute of Technology	110
The Catholic University of America	111
Cold Spring Harbor Laboratory	111
Collaborative Research, Inc.	112
The Colorado College	112
University of Colorado Health Sciences Center	113
Columbia University	113
Columbia University Law School	114
Commonwealth Scientific and Industrial Research Organization	114
Computational Biosciences, Inc.	114
The University of Connecticut	115
Duke University	116
Eunice Kennedy Shriver Center for Mental Retardation	116
Florida State University	117
Harvard Medical School	117
The Institute for Genomic Research	118
Intelligenetics Inc	119

Johns Hopkins University School of Medicine	119	Biotechnology: Medical Applications	141
University of Kansas Medical Center	119	<i>Intramural DOE Laboratories</i>	
Large Scale Biology Corporation	120	Argonne National Laboratory	141
The Library of Congress	120	Brookhaven National Laboratory	141
Linus Pauling Institute of Science and Medicine	120	Idaho National Engineering Laboratory	146
Massachusetts Institute of Technology	121	Lawrence Berkeley Laboratory	146
University of Michigan	121	Los Alamos National Laboratory	149
Molecular Dynamics	121	Oak Ridge Institute for Science and Education	151
Morehouse School of Medicine	122	Oak Ridge National Laboratory	151
National Academy of Sciences		<i>Offsite Grants</i>	152
Institute of Medicine	122	University of Alabama	152
National Institutes of Health	122	ALEM Associates	153
National Institutes of Mental Health	123	Boron Biologicals, Inc.	153
University of Medicine and Dentistry		Boston University	154
of New Jersey	123	University of California, Davis	154
State University of New York		University of California, Davis Medical Center	155
Health Science Center at Syracuse	123	University of California, Irvine	155
University of North Carolina	124	University of California, Los Angeles	
Northeastern University	124	Laboratory for Biomedical and	
University of Pennsylvania	124	Environmental Sciences	156
Promega Corporation	125	University of California, San Francisco	
Ransom Hill Bioscience	125	School of Pharmacy	158
Rhode Island Hospital and Brown University	126	University of Chicago	159
Salk Institute for Biological Studies	126	University of Cincinnati	160
Stanford University	127	Cornell University	160
University of Texas	127	Duke University Medical Center	160
Tropix, Inc.	127	Hypres, Inc.	161
University of Utah	128	University of Illinois	161
University of Washington	128	The Johns Hopkins University	
WGBH Educational Foundation	129	School of Medicine	162
University of Wisconsin	129	Massachusetts General Hospital	162
WNET/THIRTEEN	130	Massachusetts Institute of Technology	162
Biotechnology: Structural Biology	131	Massachusetts Institute of Technology	163
<i>Intramural DOE Laboratories</i>		University of Michigan Medical Center	163
Argonne National Laboratory	131	University of Missouri	164
Brookhaven National Laboratory	132	The University of Nebraska Medical Center	165
Lawrence Berkeley Laboratory	135	Ohio State University	165
Lawrence Livermore National Laboratory	137	Ohio State University Research Foundation	165
Los Alamos National Laboratory	138	University of Pennsylvania	166
Oak Ridge National Laboratory	138	The Schepens Eye Research Institute	166
Stanford Linear Accelerator Center	139	Science Research Laboratory	166
<i>Offsite Grants</i>		Sloan-Kettering Institute for Cancer Research	167
University of California, Berkeley	139	Stanford University School of Medicine	167
University of California, Davis	140	University of Tennessee	167
University of Chicago	140	University of Tennessee	167
Princeton University	140	University of Tennessee Medical Center	168
Rice University	141	University of Texas	
State University of New York at Stony Brook	141	M.D. Anderson Cancer Center	168
		Texas A&M University	168
		Thomas Jefferson University	169
		Tufts-New England Medical Center	169

University of Washington Cancer Center	169
Washington University School of Medicine	170

Environmental Research

Environmental Processes and Effects: Atmospheric Chemistry and Dynamics 171

Intramural DOE Laboratories

Argonne National Laboratory	171
Brookhaven National Laboratory	172
Environmental Measurements Laboratory	174
Lawrence Berkeley Laboratory	174
Lawrence Livermore National Laboratory	174
Los Alamos National Laboratory	175
Oak Ridge National Laboratory	175
Pacific Northwest Laboratory	176
Westinghouse Savannah River Company	178

Offsite Grants

Boston College	179
Comstock, Inc.	179
University of Minnesota	180
National Oceanic and Atmospheric Administration	180
University of Pittsburgh	181
Southwest Sciences, Inc.	181
Spectral Sciences, Inc.	182
State University of New York	182
Texas A&M University	182

Environmental Processes and Effects: Ocean Margins 183

Intramural DOE Laboratories

Brookhaven National Laboratory	183
--------------------------------	-----

Offsite Grants

Columbia University	185
Dynamics Technology, Inc.	185
Florida State University	186
Geotech Inc.	187
K.C. Research Corporation	187
Louisiana Universities Marine Consortium	187
University of Maine	188
Marine Biological Laboratory	188
Monterey Bay Aquarium	188
National Academy of Sciences	189
National Science Foundation	189
University of North Carolina at Chapel Hill	190
North Carolina State University	190
Ocean Optics, Inc.	190
University of Oregon	191
Oregon State University/University of Oregon	191
Sea Tech, Inc.	192
Skidaway Institute of Oceanography	192

University of Southern Mississippi	193
State University of New York at Stony Brook	193
Texas A&M University	194
Texas A&M University	194
Woods Hole Oceanographic Institution	194

Environmental Processes and Effects: Subsurface Sciences and Environmental Radon 196

Intramural DOE Laboratories

Argonne National Laboratory	196
Brookhaven National Laboratory	197
Idaho National Engineering Laboratory	198
Lawrence Berkeley Laboratory	199
Lawrence Livermore National Laboratory	201
Los Alamos National Laboratory	201
Oak Ridge National Laboratory	202
Pacific Northwest Laboratory	205

Offsite Grants

University of Arizona	210
University of California, Irvine	211
Colorado State University	211
Cornell University	212
University of Delaware	212
Farachem Technology, Inc.	213
Florida State University	213
Golder Associates, Inc./Idaho National Engineering Laboratory	214
University of Hawaii at Manoa	214
University of Illinois	214
The Johns Hopkins University	215
Massachusetts Institute of Technology	215
University of Michigan	215
Michigan State University	216
University of Nevada	216
New Mexico Institute of Mining and Technology	216
University of Notre Dame	218
Oregon Graduate Center	218
Pennsylvania State University	219
Physical Sciences, Inc.	219
Purdue Research Foundation	220
Rensselaer Polytechnic Institute	220
University of Tennessee	220
U.S. Geological Survey	221
U.S. Geological Survey	222
University of Virginia	223
Yale University	223

Environmental Processes and Effects:**Ecological Research 224***Intramural DOE Laboratories*

Argonne National Laboratory	224
Fermi National Accelerator Laboratory	224
Idaho National Engineering Laboratory	225
Los Alamos National Laboratory	225
Oak Ridge National Laboratory	226
Pacific Northwest Laboratory	227
Savannah River Ecology Laboratory	228

Offsite Grants

University of Alaska, Fairbanks	228
University of California, Berkeley	229
University of California, Los Angeles, Laboratory of Biomedical and Environmental Sciences	229
University of Colorado	230
Colorado State University	230
Duke University	230
Ohio State University Research Foundation	231
Princeton University	231
Stanford University	231
University of Utah	232
University of Wisconsin	232

Global Change: Climate Modeling and**CHAMMP 232***Intramural DOE Laboratories*

Argonne National Laboratory	232
Brookhaven National Laboratory	233
Lawrence Livermore National Laboratory	233
Los Alamos National Laboratory	235
Oak Ridge National Laboratory	236
Pacific Northwest Laboratory	237
Sandia National Laboratory	237

Offsite Grants

Applied Research Corporation	237
University of Arizona	238
Brown University	238
University of California, Los Angeles	238
University of California, San Diego	239
University of Colorado	239
Colorado State University	239
Columbia University	241
Columbia University	241
University of East Anglia	241
University of Illinois	242
Iowa State University	242
University of Maryland	243
University of Massachusetts	243
Massachusetts Institute of Technology	244

National Academy of Sciences	244
------------------------------	-----

National Center for Atmospheric Research	245
--	-----

National Climatic Data Center	246
-------------------------------	-----

National Science Foundation	247
-----------------------------	-----

Naval Postgraduate School	247
---------------------------	-----

New York University	247
---------------------	-----

Oregon Graduate Institute of Science and Technology	247
--	-----

Rutgers University	248
--------------------	-----

Santa Fe Institute	248
--------------------	-----

Scripps Institution of Oceanography	248
-------------------------------------	-----

State University of New York at Albany	249
--	-----

State University of New York at Stony Brook	250
---	-----

University Corporation for Atmospheric Research	250
---	-----

University of Wisconsin	250
-------------------------	-----

Global Change: Quantitative Links**and ARM 251***Intramural DOE Laboratories*

Argonne National Laboratory	251
Brookhaven National Laboratory	251
Environmental Measurements Laboratory	252
Lawrence Berkeley Laboratory	252
Lawrence Livermore National Laboratory	253
Los Alamos National Laboratory	253
National Renewable Energy Laboratory	254
Oak Ridge National Laboratory	255
Pacific Northwest Laboratory	255
Sandia National Laboratory	258

Offsite Grants

University of Alaska	259
University of Colorado	259
Colorado State University	259
Defense Advanced Research Projects Agency	260
University of Denver	260
Desert Research Institute	261
Illinois State Water Survey	261
University of Maryland	261
University of Miami	262
National Aeronautics and Space Administration	262
National Aeronautics and Space Administration	263
National Center for Atmospheric Research	263
New York University	264
Science Applications International Corp.	265
Scripps Institution of Oceanography	265
Southern Methodist University	265
State University of New York, Albany	266
Syracuse University	266
Texas A&M University	266
University of Wisconsin, Madison	267

Global Change: Carbon Cycle and Vegetation Research 267
Intramural DOE Laboratories

Brookhaven National Laboratory	267
Oak Ridge Institute for Science and Education	268
Oak Ridge National Laboratory	268
Pacific Northwest Laboratory	269

Offsite Grants

U.S. Department of Agriculture—Agricultural Research Service	270
U.S. Department of Agriculture—Agricultural Research Service	271
U.S. Department of Agriculture—Agricultural Research Service	271
University of Bern	272
University of California, Los Angeles, Laboratory of Biomedical and Environmental Sciences	272
Columbia University	272
Duke University	273
Harvard University	274
University of Illinois	275
Kansas State University	275
National Aeronautics and Space Administration	276
Natural Environment Research Council	276
University of New Hampshire	276
Princeton University	277
San Diego State University	277

Scripps Institution of Oceanography	277
Smithsonian Institution	278
University of South Carolina	278
State University of New York, Syracuse	278
Tuskegee Institute	279
Woods Hole Research Center	279

Global Change: Oceans Research 279
Intramural DOE Laboratories

Brookhaven National Laboratory	279
Oak Ridge National Laboratory	280
Pacific Northwest Laboratory	280

Offsite Grants

Columbia University	281
National Academy of Sciences	282
Scripps Institution of Oceanography	282
Woods Hole Oceanographic Institution	284

Global Change: National Institute for Global Environmental Change 284
Offsite Grants

University of California, Davis	284
---------------------------------	-----

Investigator Index 287
Institution Index 333

Legislative History

The Atomic Energy Act of 1946 (P.L. 79-585) provided the initial charter for a comprehensive program of applied and basic biological research. This act authorizes the Department to conduct research and development related to the utilization of fissionable and radioactive materials for medical, biological, and health purposes. It also provided for the protection of health during the same research and development activities. The Atomic Energy Act of 1954 (P.L. 83-703), as amended, authorized the Atomic Energy Commission "to conduct and support research and development activities, including authority to conduct research on the biologic effects of ionizing radiation" for "the protection of health and promotion of safety during research and production activities" and for "the preservation and enhancement of a viable environment."

The Energy Reorganization Act of 1974 (P.L. 93-438) specifically provided that the responsibilities of the Administrator of the Energy Research and Development Administration (ERA)

shall include "engaging in and supporting environmental, biomedical, physical, and safety research related to the development of energy sources and utilization technologies."

The Federal Non-nuclear Energy Research and Development Act of 1974 (P.L. 93-577) authorized ERA to conduct a comprehensive non-nuclear energy research, development, and demonstration program to include the environmental and social consequences of the various technologies.

The Department of Energy Organization Act of 1977 (P.L. 95-91) mandated the Department "to assure incorporation of national environmental protection goals in the formulation and implementation of energy programs, and to advance the goal of restoring, protecting, and enhancing environmental quality and assuring public health and safety," and to conduct "a comprehensive program of research and development on the environmental effects of energy technology and program."

Foreword

This report presents summaries of the research projects supported by the Office of Health and Environmental Research (OHER) during FY 1992. Part of the Office of Energy Research, OHER is the primary health and environmental research arm of the U.S. Department of Energy (DOE). The principal mission of OHER and its Biological and Environmental Research (BER) programs is to provide the scientific foundation for understanding and anticipating the long-term health and environmental consequences of energy use and development and for understanding and technologically solving major problems in biology and medicine related to these issues. The research should also provide the foundation for developing solutions to environmental problems related to energy technologies.

Two scientific areas, whose convergence will have a significant impact on the Department's missions and the implementation of the National Energy Policy Act of 1992, are undergoing a revolution today. The revolution in the biological sciences, together with the rapidly evolving power of modern technology in instrumentation and computer science, will dramatically change the practice of basic and applied science in a way that is important to the Department's fundamental concerns. The research programs outlined in this document are based on fundamental research and focused on advances in these two areas to realize the promise.

By the year 2000, the programs described in this publication can lead to greatly improved predictive capability. The most important of these enhanced predictive capabilities involve—

- Greatly improved molecular tools for health risk assessment, and the ability to predict and evaluate the impacts on human health, exposures to low levels of radiation and energy-related chemicals in the workplace and the environment, including an understanding of the basis of individual susceptibilities.
- Greatly improved understanding and ability to predict the global effects of energy-related emissions on climate and the biosphere.
- Biotechnologically enhanced, medical diagnostic, and therapeutic capabilities through integration of molecular biology, computational simulation, genetic engineering, and nuclear medicine.

These capabilities will serve the Department and the Nation well by enabling us to predict and avoid risks to human health and the environment, on the one hand, and to avoid unnecessarily conservative and costly exposure standards, regulations, and compensation litigation, on the other.

In addition, the programs will produce new tools and new scientific knowledge of wide applicability. Four particular areas present major opportunities for development—

- Fundamental research in modern biotechnology, based on the Structural Biology Program, the Human Genome Program, the Medical Applications Program, the Subsurface Science Program, and the Coastal Margins Program.
- Multidisciplinary research in global environmental change, based on the present Carbon Dioxide Research Program, and the Ecological Sciences Program.
- Exploitation for practical purposes of diverse and unique microorganisms, such as for bioremediation by microorganisms found at extended depths below the soil surface, or for novel chemical technologies.
- Computational biology and multidisciplinary research linking the revolution in biology to that in computer and information technology.

A growing recognition also exists of the environmental fragility of the planet and of the power of modern biology and biotechnology to have an impact on diverse sectors of the economy and technological base. Considered together, these prospects suggest that a cautious optimism is warranted. Addressing these issues and seizing the opportunities will require new and enhanced interdisciplinary scientific endeavors in biological and environmental research—making use of the power achieved through conjoining the disciplines of physics, chemistry, engineering, and computer science with molecular and environmental biology.

Changing world conditions are leading to re-examination of the roles and priorities for DOE laboratories. With their broad technological strengths and a diminishing role in weapons-related research, DOE laboratories are well poised to play a leading role in these new endeavors. Current programs could provide a foundation on which to build biotechnology and

environmental capabilities comparable to the national laboratories' current capabilities and strengths in the physical sciences. With concerted efforts at coordination among the several scientific sectors, these interdisciplinary efforts can then act as catalysts for similar developments in the university and industrial scientific communities.

This report provides a convenient guide to OHER-supported research for the scientists, technologists, and administrators within DOE programs, academia, professional associations, other government bodies, and the private sector seeking oppor-

tunities for research support or collaboration. Members of the legislative and executive branches of government who desire a fuller appreciation of the role and promise of DOE's mission and core capabilities in health and environmental research will also find this volume of interest.

David J. Galas, Ph.D.

Associate Director for Health & Environmental Research
Office of Energy Research

Introduction

The Biological and Environmental Research (BER) Program of OHER has two main missions: (1) to develop the knowledge base necessary to identify, understand, and anticipate the long-term health and environmental consequences of energy use and development and (2) to utilize the Department's unique scientific and technological capabilities to solve major scientific problems in medicine, biology, and the environment. These missions reflect a commitment to develop the beneficial uses of advanced energy technologies while at the same time assuring that any potentially adverse health and environmental impacts of the Nation's energy policies are fully identified and understood.

Emphasis is given to long-term research that is comprehensive and multidisciplinary in scope and quantitative and mechanistic in its approach to scientific questions. An increasingly pervasive theme in the program is the rapid accumulation of new knowledge of the molecular basis of biological processes, structures, and functions, including the areas of health effects, subsurface and ocean sciences, and nuclear medicine. Program orientation in both the environmental and health areas is directed toward the broad goals of reducing important scientific uncertainties; improving the predictability of effects for critical issues such as global climate change, indoor radon, and the health risks of low level exposures to energy-related agents; providing cost-effective solutions for dealing with environmental wastes; and producing new tools and knowledge of wide applicability by fostering research in modern biotechnology.

The BER Program includes research in atmospheric, marine, and terrestrial processes, including the linkage between the use in greenhouse gases, carbon dioxide, and regional and global climate change; in molecular and subcellular mechanisms underlying human somatic and genetic processes and their responses to energy-related environmental toxicants; in nuclear medicine, structural biology, the human genome, measurement sciences and instrumentation, and other areas that require the unique capabilities of the Department's laboratory system.

The principal areas of research are Health Research and Environmental Research.

I. HEALTH RESEARCH

A. Radiation and Chemical Effects

This research program is designed to yield experimental data needed to predict long-term health impacts on workers and the public that may be associated with energy production and use. The categories of research supported include (1) biological effects studies, (2) cellular and molecular research to provide fundamental understanding of the properties of living systems that is necessary for interpreting and extrapolating experimental health effects data, (3) radiological and chemical physics studies to determine radiation interaction mechanisms and define energy transfer and degradation processes, and (4) analytical technology to provide new measurement science concepts and improved dosimetry systems for radiation and chemical exposures.

1. Biological Effects Studies

Biological effects studies are conducted at all levels of biological organization, from molecules to whole animals, to resolve the limitations of acquiring and interpreting health data on human populations exposed to environmental agents. This research is primarily concerned with evaluating delayed types of health effects—cancer, heritable genetic damage, developmental effects, and damage to body systems (organs and their functions)—that are caused by ionizing radiation or energy-related chemicals. The advent of recombinant DNA techniques, the development of new cellular techniques and systems, and the availability of better models (transgenics and in vitro/in vivo systems) are providing new tools for understanding the fundamentals of carcinogenesis and for determining whether it is possible to differentiate between spontaneous and chemically induced or radiation-induced malignancies.

Research is primarily oriented toward defining the effects of exposure to relatively low dose and dose rates normally encountered by human populations, e.g., radon exposures, environmental cleanup operations, etc. Research and related activities are arrived at by developing comprehensive approaches for relating radon exposure and response at the cellular, molecular, and organic level. Current health risk assessments for indoor population exposures to radon are derived primarily from studies of dose-response relationships in uranium miners. Similar-

ties and differences between the exposure conditions occurring in mines and those occurring from indoor exposures (residential, etc.) are being examined. Factors being considered include age, gender, and concurrent exposure to airborne pollutants (e.g., cigarette smoke, diesel exhaust, etc.). Quantitative data and principles are being developed to reduce the uncertainties in assessing indoor radiation exposures and lung cancer risks to the public from inhaled radon and radon progeny. Radon research also aims to provide the scientific underpinning for developing radon control and mitigation strategies. This sub-program also develops information necessary to predict more accurately the roles of dose, dose rate, and ionization density (or linear energy transfer) on the induction of somatic mutations, cancer, or heritable damage in order to provide reliable derivation of risk estimates at low levels of dose and dose rate from radiation effects.

2. Cellular and Molecular Biology

Basic research in cellular and molecular biology aims to elucidate underlying mechanisms by which physical and chemical agents interfere with living processes and to interpret and extrapolate experimental health effects data. Fundamental knowledge is sought of how living systems function and how they regulate themselves, especially their protective mechanisms for preventing or mitigating the adverse effects of toxic agents. Information and technologies arising in the Human Genome Program are being developed to predict and evaluate differences in individual susceptibility to physical and chemical agents. Of particular interest are the mechanisms by which cells repair specific types of damage to their genetic systems and the genetic and biochemical characteristics that determine the susceptibility or resistance of individuals to harmful agents.

The current focus is to identify, isolate, and characterize the genes that govern the repair of DNA damage in human cells. This will define, at the molecular level, the intrinsic biological limitations for repairing damage. A corollary may be improved ability to assess the heterogeneity of radiation sensitivity in the human population and to identify individuals that are at greater risk of developing cancer or other disease following exposure (environmental, medical, or occupational) to radiation or chemicals. Molecular approaches for augmenting the efficiency of repair in test animals are also being examined, and repair-deficient animal models are being used to address the role of repair in development, aging, mutagenesis, and carcinogenesis. Another thrust of the program is the development of new cellular and molecular indices of exposure and/or effects. Such efforts to assign exposure dose retrospectively are critical for evaluating effects from accidental or long-term, low level radiation and/or chemical exposures. Chromosome-specific painting techniques and automated cytogenetics instrumentation coming from the Human Genome Program are providing improved biological dosimetry and sensitive new measures for detecting damage in human cells.

3. Physical and Chemical Processes

Radiological and chemical physics research is conducted into the fundamental mechanisms by which radiation interacts with biological systems and the processes whereby the deposited energy is converted into biologically active species. Chemical physics research investigates ion-molecule interactions and explores biomolecular energy degradation processes. Theoretical research in quantum biology provides a theoretical foundation for determining conformation and configuration changes in biomolecules, such as DNA, due to the interactions of physical and chemical agents.

4. Instrumentation Research

Research in support of analytical technology is providing new measurement sciences concepts and improved dosimetry systems for detecting and quantifying the presence of radiation and chemical agents in the environment and more reliably defining human exposures. Such advances support BER Program needs in environmental research, health effects studies, structural biology, and nuclear medicine.

B. Biotechnology

The missions of the BER Program encompass several major areas of opportunity for capitalizing on the enormous potential for future scientific and technological developments in the life sciences. The BER Program is increasingly oriented toward taking advantage of the promise of biotechnology and its related scientific disciplines to achieve long-term program goals. Major categories of this research effort include the Human Genome Program, the Structural Biology Program, and the Medical Applications Program. Additional biotechnology research is conducted within the health effects area (molecular and cellular biology) and in the environmental sciences (subsurface sciences and oceans research).

1. Human Genome

The aim of the human genome research is to develop the resources and technologies needed to describe the human chromosomes at the molecular level and to make significant contributions toward completing the mapping and sequencing of the human chromosomes. Current goals are (1) development of technologies to carry out more efficient and cost-effective sequencing of chromosomal DNA; (2) construction of physical maps made up of ordered DNA fragments for each human chromosome; and (3) development of necessary databases and tools for data management and analysis. Ethical, legal, and social issues related to the application of information from this research are also being addressed. Results of this work will provide the ultimate structure of the human genetic apparatus and, therefore, the basis for improved risk estimates, detailed understanding of the mechanism of mutagenesis and carcinogenesis, and the assessment of individual sensitivities to low levels of exposure to physical and chemical agents. This new molecular level information will also

significantly affect the biomedical, microbiological, and biotechnology communities by providing new resources and technologies; similarly, the advances will open new avenues for technology transfer from the Department's laboratories. The DOE program is planned and carried out in coordination with the National Institutes of Health (NIH), and is focused toward developing capabilities and tools, constructing maps, and sequencing human chromosomes, while the NIH effort is oriented toward genetic mapping and characterizing disease-related genes by exploiting both human and nonhuman model systems.

2. Structural Biology

Structural biology research takes advantage of unique resources at the Department's laboratories and the tools of modern science to enable major advances in the understanding of the relationship between macromolecular structure and biological function. Such understanding is critical to advancing the biotechnology missions of the Department over a wide range of areas of application, from energy production from biomass to environmental remediation. DOE has a special responsibility in structural biology for making available to the national scientific community cutting-edge facilities for research at the Department's major facilities, such as synchrotrons and neutron beam sources and special microscopes with analytical and high resolution capabilities. The powerful new tools and approaches used in structural biology research—such as recombinant DNA technology, site-directed mutagenesis, rapid structural determination with sophisticated equipment, powerful computer and graphics technologies, and molecular simulation—have arisen from the influx into the biological sciences of methods, technologies, and research findings of physics, chemistry, computer and information science, engineering, and mathematics. BER program commitments to support the construction of dedicated biomedical beam lines at the Advanced Light Source at Lawrence Berkeley Laboratory and the Advanced Photon Source at Argonne National Laboratory will provide unique capabilities for structural biology experiments using imaging, crystallography, small-angle scattering, as well as spectroscopy with ultrabright x-ray beams. These new facilities when completed will play an essential role in the development of structural biology as an enabling foundation for biotechnology and biomedical science. The DOE program envisions increased support for operation of user stations for structural biology and also places a high priority on training of a new generation of biologists in this rapidly evolving field.

3. Medical Applications

Medical applications research emphasizes development of advanced technologies for fundamental medical research, diagnosis, and treatment of human disease including cardiopulmonary disease, neurological disorders, cancer, and metabolic disorders. The focus is on developing—

- New approaches to radio-isotope production.

- Rapid synthesis of new radiopharmaceuticals with better physiological distribution properties including labeled compounds for boron neutron capture therapy.
- Medical imaging instrumentation, particularly for single photon and positron emission tomography to achieve higher spatial resolution and more accurate quantitation of organ physiology.
- Clinical feasibility studies including application of radio-labeled monoclonal antibodies to extend the basic findings from the research laboratory toward the initial investigation of applicability in human patients.

A new focus is molecular nuclear medicine, which will apply the concepts, resources, and technologies being developed in structural and molecular biology and human genome research to the study, diagnosis, and treatment of disease.

II. ENVIRONMENTAL RESEARCH

The goal of this program is to provide the foundation for understanding the effects of energy-related activities on the environment. An objective of the program is the integration of human-induced and natural processes to provide resolution for energy-related environmental problems. Elements of the program also address the national and international concerns regarding global environmental change. To achieve the program objectives, comprehensive research in space, atmospheric, terrestrial, subsurface, and oceanic systems is conducted in different regions of the world. For maximum cost and scientific effectiveness, most of the research is organized into multidisciplinary, multi-institutional programs. The programs cover all environmental aspects of the physical and biological sciences.

A. Environmental Processes and Effects

Research includes defining the transport, transformation, and fate of energy byproducts in atmospheric, terrestrial, subsurface, and marine systems and also identifying the major routes and rates of transfer of these byproducts through physical and biological pathways. New program dimensions address (1) the role of molecular biology in understanding the oceanic, terrestrial, and subsurface ecosystem responses and (2) the opportunity for biotechnology developments. Natural and energy-related stresses are studied from the subcellular level to the ecosystem level to determine the rates and mechanisms by which populations and ecosystems disturbed by energy activities adapt or react to these stresses. Categories of research conducted include the following:

1. Atmospheric Chemistry and Dynamics

Research in the atmospheric sciences concentrates on the transport and transformation of energy-related emissions in the atmosphere. The research improves the understanding of meteorological, chemical, and physical processes that influence the transport, transformation, and fate of gaseous and particulate species emitted to the atmosphere. The atmospheric chemistry emphasis is placed on the aqueous phase processes such as in-cloud chemical reactions and precipitation scavenging. Studies of flows in complex terrain are aimed toward improving models used in emergency preparedness and emergency response. Also being studied are processes involved in stratospheric ozone depletion.

2. Ocean Margins

The goal of this program is to determine whether continental shelves are quantitatively significant in removing carbon dioxide from the atmosphere and isolating it via burial in sediments or export to the interior ocean. Research is directed toward quantifying the mechanisms and processes by which carbon dioxide is assimilated, transported, and transformed in the coastal ocean and toward defining ocean-margin sources and sinks in global biogeochemical cycles.

3. Subsurface Science and Environmental Radon

Long-term basic research is conducted in the Subsurface Science Program on (1) the fundamental physical, chemical, and biological mechanisms that control the reactivity, mobilization, stability, and transport of chemical mixtures in subsoils and groundwater; (2) hydrogeology, including the hydraulic, microbiological, and geochemical properties of the subsurface that affect chemical mobility and stability, including numerical (predictive) modeling of coupled hydraulic-geochemical-microbial processes; and (3) the microbiology of deep sediments and groundwater. The research is focused on basic scientific understanding that will lead to cost-effective and scientifically valid solutions to the Department's long-term needs in environmental restoration, particularly at the Department's sites.

Environmental research efforts within the Radon Research Program are directed toward (1) characterizing the availability and emanation potential of radon within soils, (2) defining the environmental variables that control radon transport within soils and its movement into homes, (3) developing predictive models to link environmental transport with indoor radon levels, and (4) identifying areas that may be affected by elevated levels of indoor radon.

4. Ecological Research

The focus of this research is to understand the biological and ecological processes that control ecological responses to energy-related environmental changes. This knowledge may be used to enhance the self-adjusting processes operating within ecological systems that in turn provide sustainable natural

resources. Research activities include detecting, monitoring, and understanding ecological responses to environmental changes; developing new technologies to measure the ecological responses and uncover the detailed mechanisms; and developing methods of critically enhancing and integrating self-adjustment processes in ecosystems to resolve energy-related environmental problems.

B. Global Change

The mission of the Department's Global Change Research Program (GCRP) is to estimate the future levels and rate of increase in atmospheric carbon dioxide and other energy-related emissions and to understand and predict potential effects of emissions on climate and biota. This information is required to provide a scientific underpinning for energy policy options aimed at preventing, mitigating, or adapting to increasing greenhouse gas concentrations and to global environmental change. This program will (1) elucidate the processes controlling the global carbon cycle and predict future levels of atmospheric carbon dioxide; (2) determine how changes in concentration of greenhouse gases may change the Earth's radiation balance; (3) acquire the data and develop the models to determine how changes in the Earth's radiation balance may change climate at global and regional scales and predict rates of climate change; and (4) develop the scientific methodology to determine and quantify the combined effect of climate change and greenhouse gas concentrations on the biosphere. The principal objective of the Department's GCRP is to improve as rapidly as possible the capability to predict regional and global climate change. Categories of research conducted include the following:

1. Climate Modeling and Computer Hardware, Advanced Mathematics, and Model Physics

To develop the tools necessary to predict accurately the global regional climate change induced by increasing atmospheric concentrations of carbon dioxide and other greenhouse gases, a core research program is supported on modeling of climate change, with attention to the coupled climate system of the atmosphere, ocean, biosphere, and cryosphere. A key element is support of the program for Climate Model Diagnosis and Intercomparison [including the international general circulation model (GCM) intercomparison studies], whose work includes the study of clouds and the regional/interannual climate sensitivity to greenhouse gases. Climate model development also improves linkage of biosphere-climate and ocean-climate feedbacks for representing land/atmosphere/ocean energy and water flux.

The objective of the Computer Hardware, Advanced Mathematics, and Model Physics (CHAMMP) Program is to accelerate and improve predictions of the future response of global and regional climates to the increasing atmospheric concentrations of carbon dioxide and other greenhouse gases. Developing an Advanced Climate Model will require use of computers

capable of increasing throughput by a factor of at least 10,000, mathematical formulations and software that utilize the extensive parallelism of the emerging generations of computers, and improved algorithms that have been more thoroughly verified using more comprehensive sets of field observations than ever before.

2. Quantitative Links and the Atmospheric Radiation Measurement Program

To link quantitatively the predicted global and regional climate changes with observed changes in measurable Earth system properties, a core research program is maintained to develop the paleo, historical, and modern data sets essential for model verification and climate change detection.

The objectives of the Atmospheric Radiation Measurement (ARM) Program are—

- To describe quantitatively the radiation balance from the surface to the top of the atmosphere and determine the atmospheric characteristics responsible for this balance.
- To improve the parameterization of the formation and evolution of clouds in climate models.
- To create an experimental testbed for testing process models used in GCMs.
- To support satellite ground truth measurements.

The research involves a network of ground-based remote sensing instruments along with campaign studies using aircraft and tethered platforms. ARM focuses on quantitative links between greenhouse gases and climate change and examines climate feedbacks and energy fluxes in the coupled land/atmosphere/ocean system. In addition, the research examines atmospheric cycling and transformation of radiatively and chemically important trace species.

3. Carbon Cycle and Vegetation Research

Research in the Global Carbon Cycle Program supports measurement and modeling activities to estimate changes in the physical, chemical, and biological processes controlling sources and sinks of carbon dioxide. Measurement of carbon dioxide fluxes between atmosphere, biosphere, and land and ocean surfaces, and of cycling of carbon within the terrestrial biosphere and the oceans is required in order to predict atmospheric carbon dioxide change in relation to the release from burning fossil fuel and deforestation. DOE's unique research on plant response to variable carbon dioxide concentrations is focusing increased attention on plant carbon metabolism, specifically to address basic biological mechanisms that affect direction, rate, and magnitude of carbon dioxide fluxes and biotic responses to carbon dioxide enrichment. The scope includes work on carbon dynamics of terrestrial, aquatic, and marine environments to

quantify source and sink strength of vegetation, soil, and sediments for carbon.

4. Oceans Research

The Oceans Research Program supports a global survey of carbon dioxide in the ocean and studies to improve ocean circulation models used for climate research. The research involves integrated laboratory, observational, and modeling studies to understand mixing, transport processes, and carbon cycling in the ocean and the exchange of heat and carbon between the ocean and the atmosphere. As part of the U.S. Global Change Research Program (USGCRP), the DOE Oceans Research Program is focused on central questions of uncertainties about the rates of carbon and heat transport in the ocean and changes in the oceanic carbon dioxide reservoir. It is a critical component of the biogeochemical and ocean dynamics elements of USGCRP.

5. National Institute of Global Environmental Change

The National Institute of Global Environmental Change (NIGEC) is an initiative created by Congress in 1989 to support DOE's Global Change Research Program primarily by providing funding for scientists in the academic community. Proposals submitted to NIGEC through the five regional centers are to address primarily the high priority areas in DOE's Global Change Research Program. The NIGEC goal for allocation of funding is 75 percent for scientific aspects of global environmental change, 20 percent for research on policy options and strategies, and 5 percent on educational efforts. NIGEC is operated for DOE by the University of California (UC) at Davis under a cooperative agreement. It consists of five regional centers (Northeastern Center at Harvard, Midwestern Center at Indiana University, Southeastern Center at the University of Alabama, Southcentral Center at Tulane, and the Western Center co-hosted by UC, Davis and UC, Irvine). Research supported through NIGEC includes projects that span a range of priorities in USGCRP.

BER Program

Role Is Unique

The BER Program role and framework is unique among Federal agencies and has a long and rich record of achievement. Program resources are increasing in the face of fiscal constraints and must be carefully managed and justified by the OHER technical staff. But program advances require the continuous infusion of innovative ideas from productive investigators. The compilation of BER project descriptions has been organized to help current and prospective research participants to better understand the scope and focus of the present BER programs and how they might fit in to meet future challenges.

No other Federal program pursues the same comprehensive goals as OHER's program; most Federal programs focus only on selected facets of energy-related issues relevant to their missions in either health and environmental or physical re-

search. Although mission oriented, OHER's program places heavy emphasis on basic research. It evaluates the health and environmental consequences of energy activities within the context of overall ecosystems and at all levels of biological and physical organization. It addresses long-term generic issues, rather than the near-term questions that are the focus for the regulatory community or industry. Thus, OHER takes an anticipatory rather than a regulatory approach toward identifying and solving potential health and environmental problems. It relies on multidisciplinary teams of individuals in unique dedicated research facilities and on the expertise of hundreds of investigators throughout the scientific community.

The national laboratories and other onsite specialized laboratories supported by OHER represent an important national resource of skilled investigators; advanced major scientific instrumentation; and exceptional, specialized, often unique, research facilities. The laboratories are able to address the diversity of research issues described in this program while providing additional benefits to the scientific community at large.

But success in meeting OHER's wide range of programmatic objectives requires contributions from each of the three components of the Nation's research community: the national laboratories, the universities, and the private sector. This Office supports research in each of these sectors and encourages cooperation among them. More specifically, OHER has an active program among the three components to encourage transfer of the tools and technologies resulting from its research program. It also fosters the development of future health and environmental sciences manpower by supporting universities as appropriate; facilitating access to advanced, unique facilities at the national laboratories for research and training; encouraging collaborative research and development agreements between the laboratories and industry; and sponsoring education and training programs.

International cooperation remains an important priority for OHER because many of the problems to be evaluated are of worldwide importance and are most efficiently and effectively investigated by collaborative effort. OHER also maintains extensive coordination with other Federal agencies in areas of mutual interest to prevent unnecessary overlap and yet minimize the possibility of important gaps in effort.

The Past Achievements Are Significant

In working toward its program goals, OHER has contributed significantly to progress in health and environmental science. It has promoted the groundwork for new disciplines that offer fresh approaches to important problems. Under the programs of DOE's predecessors, radiobiology, radioecology, and health physics matured together with nuclear medicine, which aimed at applying new tools of radiation and radioactivity to the relief of human suffering. Genetics and biology were enriched with powerful techniques and devices, allowing scientists to delve into increasingly deep levels of biological organization, to

uncover the molecular events responsible for biological damage, and to provide insights into repair and recovery processes. Extensive studies on human populations exposed to radiation, especially A-bomb survivors in Hiroshima and Nagasaki and radium-dial painters, have provided quantitative estimates of human cancer risk from this source. These estimates are much more precise than the assessments for any other environmental carcinogen. Databases, research designs, and models developed during decades of atmospheric, terrestrial, and aquatic research continue to yield dividends in time and money saved. Measurement concepts and devices such as flow cytometry, positron emission tomography, and resonance ionization spectroscopy, in concert with advances in lasers and new isotopes, are used in a broad range of applications. These applications aim to produce human gene libraries, study genetic disease, detect DNA lesions produced by carcinogens, and distinguish mental disorders, and coronary bypass candidates in the elderly as well as to measure oceanic circulation and date groundwater for waste isolation. Proposed in FY 1986 and begun in FY 1987, the Human Genome Initiative is widely recognized by the scientific community here and abroad because it addresses one of modern biology's most significant challenges. In short, the research results to date are vast, varied, and exciting; these results promise that DOE's large scale, multidisciplinary approach will continue to provide a sound basis for future achievements, surpassing those of the past.

Program Resources Are Increasing

The program for FY 1992 was supported by a budget of \$310.8 million (excluding \$41.6 million provided for Congressionally mandated projects), allocated to various subprograms as shown in Table 1. About 69 percent of the research effort was conducted in Government-owned, contractor-operated facilities, otherwise designated as onsite laboratories. Most of the remaining funds were expended offsite, in support of some 400 research awards to more than 175 universities, hospitals, and research organizations in the private and public sectors. University-based research, whether on or offsite, received more than 33 percent of the budget for research effort.

Onsite projects generally are funded at the outset of each fiscal year, i.e., October 1. However, laboratory directors have some flexibility to mobilize resources during the year to better achieve program objectives. Therefore, levels of effort presented for the onsite projects may not reflect exact actual expenditures, but are initial budget projections including overhead costs. FY 1992 budget allocations to each laboratory are indicated in the section "Research Profiles of Major OHER-Supported Programs at DOE Facilities." Offsite support levels tend to be lower, reflecting differences in the relative level of effort expended on each project. Offsite grantees invariably provide only a fraction of their time due to other commitments, including teaching and other research. At DOE laboratories, the investigators are generally more fully engaged in a project, often in a group effort; hence, the scope and funds assigned to such projects tend to be greater than those assigned to offsite projects.

Table 1. Biological and Environmental Research Budget (\$ Millions)

Program Area	Appropriated	
	FY 1992	FY 1993
I. Health Research	\$170.9	\$186.8
A. Radiation and Chemical Effect	<u>70.3</u>	<u>72.3</u>
1. Biological Effect Studies	29.9	31.7
2. Cellular and Molecular Biology	21.7	22.3
3. Physical and Chemical Processess	5.9	6.7
4. Instrumentation Research	12.8	11.6
B. Biotechnology	<u>100.6</u>	<u>114.5</u>
1. Human Genome	56.7	62.2
2. Structural Biology	11.4	16.3
3. Medical Applications	32.5	36.0
II. Environmental Research	109.7	123.2
A. Environmental Processes and Effects	<u>36.1</u>	<u>40.8</u>
1. Atmospheric Chemistry and Dynamics	10.2	10.6
2. Ocean Margins	6.1	7.7
3. Subsurface Science and Environmental Radon	14.0	16.0
4. Ecological Research	5.8	6.5
B. Global Change	<u>73.6</u>	<u>82.4</u>
1. Climate Modeling and CHAMMP	21.1	22.9
2. Quantitative Links and ARM	25.2	29.2
3. Carbon Cycle and Vegetation Research	11.7	13.7
4. Oceans Research	4.7	5.6
5. NIGEC	10.9	11.0
III. Other	71.8	46.8
A. Capital Equipment and Construction	24.1	26.4
B. Program Direction	6.1	6.6
C. Congressionally Mandated Projects	<u>41.6</u>	<u>0.0</u>
Total	\$352.4	\$342.9

In FY 1992, other Federal, state, and local agencies and private industry invested more than \$160 million at onsite facilities for health and environmental research. Many BER-funded scientists in the onsite laboratory program also hold academic appointments and serve as an important resource in the formal education of the Nation's scientists, engineers, and physicians. The research projects supported at the DOE labo-

ratories also serve as vehicles for training some 400 graduate and undergraduate students and postdoctoral investigators, with a comparable number participating in offsite grants to universities and other institutions. In addition, three postdoctoral fellowship programs have been initiated since 1986. These include the Alexander Hollaender, Human Genome, and Global Change Distinguished Post-Doctoral Fellowship Programs. Each is designed to attract superior young scientists to OHER-sponsored laboratories. The fellowships enable up to 25 exceptionally talented recent graduates to pursue their research interests at one of OHER's major laboratory programs for up to 2 years, with annual stipends between \$35,000 to \$40,500. These laboratory programs also provide opportunities for research collaboration by some 150 full-time visiting scientists as well.

The laboratories' unique facilities and research instrumentation attracted more than 1,200 part-time users from the scientific community. Innumerable collaborations also exist between onsite investigators and the scientific community in this country and abroad.

The result of OHER research is primarily state-of-the-art information, which is widely disseminated. Scientists supported by the program make nearly 2,000 presentations each year at technical meetings and document their work in books, reports, and in more than 2,500 refereed journal articles.

OHER Staff Scientists Manage the BER Program

Because of the multidisciplinary nature of the program, OHER is organized and managed along disciplinary lines. It consists of three divisions (Table 2) with a total professional staff of 39 that includes specialists in biochemistry; biophysics; molecular and cellular biology; genetics; toxicology; radiation biology; health physics; nuclear medicine; physiology; engineering; analytical, physical, and organic chemistry; atmospheric sciences; ecology; geology; oceanography; and related disciplines.

Headquartered in Germantown, Maryland, OHER technical staff are responsible for program management, planning, and development. They establish strategy, priorities, and schedules; define resource allocations; conduct program reviews and evaluations; and maintain close liaison with other DOE programs, Federal agencies, Congress, and the scientific community.

New Ideas by Bench Scientists Determine Progress

Like any other large scale research program, OHER varies its activities from year to year as existing projects end and new program initiatives or lines of investigations open up. New ideas and expertise are the lifeblood of all research programs. Grant applications to address scientific objectives for different program areas are invited periodically by announcements in the *Federal Register*. The program recommends submission of a two-page preliminary proposal briefly describing the research project and the proposed level of funding to determine whether the preparation of a more detailed formal proposal is warranted.

Table 2. Program Organization

Information about development and submission of applications, eligibility, limitations, evaluation criteria, selection process, and other policies and procedures may be found in DOE booklet DOE/ER-0249, "Application and Guide for the Special Research Grant Program, 10 CFR Part 605." Copies may be requested by phoning the relevant division listed in Table 2 or writing them at the following address:

Office of Health and Environmental Research
Office of Energy Research
U.S. Department of Energy
Washington, DC 20585

The technical merits of applications submitted in response to a program opportunity notice are evaluated by teams of experts convened for the review from all sectors of the scientific

community. New applications and requests for renewal of ongoing research (generally after each 3-year period of support) compete for the available funds. Research proposals from onsite institutions and offsite grant applications are reviewed under separate domains and budget allocations. OHER program managers are responsible for selecting which research projects to support, based on technical merit, program relevance, and cost. Requests for support of workshops and conferences are considered year round and reviewed primarily by OHER program staff.

OHER staff will also be pleased to answer telephone questions about the program in general or about specific projects. For technical exchange with an investigator, researchers may call the investigator directly.

Report Format Should Help Identify Role for Participants

The project summaries in this report have been organized to reflect the program's major themes and focus. An overview of the research categories is presented in the next section to provide a perspective of the range of projects. Within each research category, project summaries are divided into efforts performed in DOE laboratories (onsite laboratories) and those performed elsewhere (offsite grantees). In both cases, the abstracts are presented in alphabetical order by institution and then by investigator. Profiles for the larger OHER-supported programs at DOE facilities are presented in the section beginning on page xxxv to provide a perspective on their respective program roles, research interests, and physical resources. Finally, indexes by investigator and institution are provided; they are coded by summary numbers that run sequentially throughout the report.

Despite the report's length, this compilation of project titles and summaries is still a relatively superficial source of information. More substantive information is contained in detailed research proposals, progress reports, published data, facilities, and from the cadre of talented and experienced investigators and supporting personnel conducting the research. This report provides, at best, an overview of activities and offers a means of developing a dialogue in areas of mutual interest. We welcome your comments and inquiries.

Murray Schulman, Ph.D.

Executive Assistant to the Associate Director
Office of Health and Environmental Research
Office of Energy Research

Research In Progress: Overview

The OHER Program supports research that provides the scientific and technical knowledge needed to solve important problems in the biological, medical, and environmental sciences. The program uses the unique multidisciplinary research capabilities and facilities of the national laboratories. It supports faculty and students from universities and investigators from industry and other Federal agencies throughout the United States in their efforts to conduct research aimed at resolving health and environmental issues while strengthening U.S. energy security and economic growth.

The Health Research Program involves two major components. The first, Radiation and Chemical Effects, develops new quantitative data, principles, and models to reduce the uncertainty in assessing the health risks of radiation and chemical exposure to workers and the public which results from energy development and use. The second component, Biotechnology, includes programs in structural biology, the human genome, and medical applications that exploit the Department's capabilities and facilities to provide infrastructure and technologies crucial to advancing the U.S. biotechnology industry. These programs include employing studies of the relationship between molecular structure and function of macromolecules such as proteins; developing the resources and technologies needed to construct maps and determine the sequence of the 3 billion DNA subunits that comprise the genetic code of the 24 different human chromosomes; and interfacing developments in molecular biology and structural biology with nuclear technology and imaging sciences to create new medical applications for the study, diagnosis, and treatment of disease.

The Environmental Research Program also has two main components. The first, Environmental Processes and Effects, addresses issues ranging from environmental restoration at contaminated DOE facilities to atmospheric studies of processes affecting the distribution of ozone. A common goal is to quantify how energy-related agents move through, impact, and are changed by the atmosphere and marine ecosystems. A terrestrial transport program focuses on understanding the fundamental physical, chemical, and microbiological mechanisms that control the reactions of organically complexed radionuclides; this knowledge provides a basis for new cleanup technologies. Research efforts also focus on isolating and determining the origin and physiology of bacteria discovered by DOE at

depths of more than 3,000 meters and the mechanisms of their deep transport and/or in situ survival.

Marine research is turning to understanding how organisms affect the cycling of carbon on continental shelves. A new Program for Ecosystem Research is providing a basis for understanding ecosystem adjustments to environmental changes resulting from energy-related activities.

The second component is the Department's Global Change Research Program, which is part of the Federal program coordinated under the Committee on Earth and Environmental Sciences of the Office of Science and Technology Policy. The OHER program role is to provide quantitative information for predicting the future atmospheric concentrations of carbon dioxide and other energy-related greenhouse gases and the rate and magnitude of potential climate change and to understand and predict their impact on ecosystems. Such information will enhance the scientific basis for responsible policy decisions.

The principal areas of research are Health Research and Environmental Research.

I. HEALTH RESEARCH

A. Radiation and Chemical Effects

The mission of this program area is to provide the basis for improved risk estimates for human long-term health effects following exposure to low level radiation, including radon and chemicals. Advances are achieved by—

- Utilizing experimental biological systems from molecules to intact organisms to identify mutagenic and carcinogenic consequences.
- Characterizing the biological and biochemical mechanisms for their repair and impact.
- Improving methods for predicting human health risk by developing biomarkers of exposure, susceptibility, and disease.

- Describing the radiological and chemical physics during the initial events following exposure.
- Developing new measurement concepts and dosimetry to detect, measure, and characterize radiological and chemical hazards.

1. Biological Effects Studies

Although epidemiological studies have long provided important data for estimating the upper limits of risk for selected exposure conditions, they have limited use at low doses and dose rates. In these cases, cellular and animal model systems can provide the experimental flexibility needed to establish the principles underlying molecular, biochemical, and cellular responses to exposure to energy-related agents. The majority of biological effects research can be broadly categorized into three areas: mutagenesis and carcinogenesis, radon, and factors influencing biological responses.

a. Mutagenesis and Carcinogenesis

Research is conducted to study the mutagenic and carcinogenic effects of energy-related radiation and chemicals in humans and laboratory animals using both in vivo and in vitro approaches. The goal of these studies is to elucidate the molecular and cellular events underlying both spontaneous and induced genetic and epigenetic events that lead to cancer, heritable mutations, and/or congenital malformations. Research approaches incorporate recombinant DNA techniques and new cellular techniques and systems with an emphasis on the use of human cells and tissues, the use of new models, e.g., transgenic animals and in vitro/in vivo systems. This work emphasizes correlations and extrapolations between animal and human data, with emphasis on the effects of low dose or low dose rate radiation exposures. Understanding the mechanisms of cancer development or the nature of specific genetic changes involved will improve our ability to estimate the cancer risk from exposure to energy-related agents.

Examples of mutagenesis and carcinogenesis research include studies to—

- Determine the role of specific oncogenes and tumor suppressor genes in the development of cancer and the nature of specific genetic changes in those genes in tumors.
- Quantify the frequency of and characterize the nature of mutations in people exposed occupationally or medically to known or potential mutagens.
- Identify, map, and characterize germ-line mutations in mice and use that information to identify human homologues of those mouse genes.
- Compare mechanisms of cell transformation in vitro and carcinogenesis in vivo to determine the validity of using in vitro models to study carcinogenesis.

b. Radon

Research is conducted to develop a comprehensive approach for relating radon exposure and dose at the cellular, molecular, and organic level and for determining its biological effects. Research efforts include (1) studying the physical and chemical behavior of radon and radon progeny, (2) characterizing radiation exposures from environmental radon, and (3) estimating the cancer risk from radon exposure. This research is developing quantitative data and principles that will reduce the uncertainties in assessing indoor radiation exposures and lung cancer risks to the public from inhaled radon and radon progeny. It also provides the scientific underpinning for developing radon control and mitigation strategies.

Examples of radon-related research include studies to—

- Identify factors that affect exposures of people to environmental radon such as radon entry into buildings and the formation and behavior of radon-associated aerosols.
- Characterize factors affecting the radiation dose from exposure to radon such as inhalation of radon-associated aerosols, deposition of those aerosols in the respiratory tract, estimation of the resultant radiation dose to the respiratory epithelium, and the effect of cigarette smoking on radiation dose.
- Identify and characterize the cells in the respiratory tract at risk for radon-induced cancer.
- Link the development of lung cancer in uranium miners and the development and use of molecular markers for identifying malignant and premalignant stages of lung cancer in people.
- Develop better models linking exposure to radon and cancer risk.

c. Factors Influencing Biological Responses

This research is aimed at developing information necessary to predict more accurately the roles of dose, dose rate, and ionization density [or linear energy transfer (LET)] on the induction of cancer, mutations, or heritable damage. This information is needed to reduce uncertainties associated with current estimates of radiation risk because estimates of risk (and exposure standards) from these exposures are based on the assumption that the frequency of adverse health effects induced by low level, environmentally relevant radiation increases linearly at any radiation dose. Estimates of risk therefore have historically been based on extrapolations from high level human or animal exposures, because the effects of extremely low dose and low dose rate radiation cannot be adequately measured.

Research includes studies to identify and characterize specific radiation-response genes and gene-specific damage induced by radiation or chemicals; characterize cellular responses to low doses of radiation; and determine the mechanism of the repair of DNA damage.

2. Cellular and Molecular Biology

Support for cellular and molecular biology research is aimed at obtaining insights into the mechanisms whereby radiation and energy-related chemicals produce biological damage and determining how such damage is repaired, transmitted into observable end effects such as mutations and cancer, or provide an early indication for exposure and injury. The majority of these research efforts can be broadly categorized into five areas: DNA repair; mutagenesis and carcinogenesis; regulation of cell proliferation, differentiation, and gene expression; damage responses; and structure/function relationships.

a. DNA Repair

Research is conducted to identify, isolate, and characterize the genes that govern the repair of DNA damage in human cells. This knowledge will define, at the molecular level, the intrinsic biological limitations to repairing damage. A corollary is to achieve the ability to assess the heterogeneity of radiation sensitivity in the human population and to identify at-risk individuals. Molecular approaches toward augmenting the efficiency of repair genes are now possible. Animal models for repair deficiency are used to address the role of repair in development, aging, mutagenesis, and carcinogenesis.

Examples of DNA repair research include studies to—

- Examine interindividual variability in DNA repair capabilities in people.
- Characterize and/or clone human or rodent genes involved in recombination repair, excision repair, and double-strand break repair.
- Characterize and clone genes responsible for ataxia telangiectasia—a human genetic disease associated with (1) an increased likelihood of developing some types of cancer and (2) an unusual sensitivity to ionizing radiation.

b. Mutagenesis and Carcinogenesis

Research is conducted to study several aspects of the mutagenic effects of energy-related radiation and chemicals. This includes research to characterize the nature of exposure-induced and spontaneous mutations in people and cultured human cells and to elucidate mechanisms involved in carcinogenesis. Understanding the mechanisms of cancer development or the nature of specific genetic changes involved will improve the ability to estimate the cancer risk from exposure to energy-related agents.

Examples of mutagenesis and carcinogenesis research include studies to characterize the mutational spectra, e.g., deletions, point mutations, etc., induced by exposures to different radiation and chemicals; identify the DNA lesions responsible for developing these different mutations; determine the germinal mutation rates induced by exposures to radiation and chemicals; determine the mechanisms of carcinogenesis in the livers of transgenic mice and of transformation in cultured

human fibroblasts; characterize the relationship between chromatin structure and responsiveness to carcinogens; determine the origin and role of karyotypic instability in carcinogenesis; and define the role of specific genes in carcinogenesis.

c. Regulation of Cell Proliferation, Differentiation, and Gene Expression

Understanding alterations in normal cellular processes that occur in response to radiation or chemical exposures requires an understanding of the mechanisms that normally regulate those processes. Knowledge of the alterations in cell proliferation, in cell and tissue differentiation, and in the expression of a variety of genes involved in tumorigenesis will be an important step toward identifying mechanisms that normally regulate those processes that occur during the initiation and development of cancer.

Examples of cell proliferation, differentiation, and gene expression research include studies to—

- Characterize mechanisms regulating the cell cycle including the role of specific genes, growth factors, second messengers, etc.
- Characterize mechanisms that can alter gene expression, e.g., methylation and phosphorylation.
- Identify and characterize tissue- or gene-specific responses to radiation or chemical exposures.
- Characterize normal DNA/protein interactions.

d. Damage Responses

Research is conducted to study initial molecular-, cellular-, and tissue-level responses to radiation and chemical exposures. Research on the nature of and mechanisms responsible for specific biological responses to radiation and chemicals provides information needed to develop biological markers to identify and quantify previous exposures and to identify individuals with increased sensitivity compared to the general population. This information is useful in estimating health risks for exposed individuals.

Examples of damage response research include studies to identify and characterize the induction of damage response and growth arrest genes; quantify and characterize exposure-induced DNA damage and chromosome aberrations; determine the role of DNA sequence in regulating the sensitivity of and response to specific radiation or chemical exposures; and determine the nature and mechanisms of damage to the lung and respiratory tract from inhaled materials.

e. Structure/Function Relationships

Understanding the mechanisms that regulate gene expression or that control cell proliferation or cell or tissue differentiation requires information on processes involved in the interaction of molecules at the tissue, cell, and gene levels. One aspect of

these important molecular interactions is the relationship between the specific structure of a molecule and its ability to interact effectively with other molecules.

Examples of structure/function research include studies on structure/function relationships for molecules involved in both specific enzymatic processes, such as photosyntheses and carbohydrate metabolism, and in specific ligand-receptor reactions, such as those involving antibodies or growth factors. Critical sites on the molecules of interest are identified, and the effect of alterations of these sites, e.g., through site-directed mutagenesis, is determined.

3. Physical and Chemical Processes

This program investigates basic physical and chemical processes initiated by interaction of ionizing radiation with matter. Emphasis is placed on identifying those processes that might be most relevant for understanding the basic mechanisms of biological action. For this reason, the program is enhancing research to attain fundamental knowledge on the physical and chemical processes involved in the interactions of energy-related agents both ionizing radiation and chemical with biologically relevant materials. Interaction products such as ionizations, excitations, and radicals are considered the initial determining factors in the ultimate biological response. Spatial and temporal distributions of interaction products in biologically relevant molecules such as DNA, proteins, lipids, and other structures in the natural environment of the cell are investigated to determine where and how the initial biologically significant lesions are formed. The program is multidisciplinary in nature and attempts to integrate the fields of physics, chemistry, and biology to develop biophysical models for predicting the health risks associated with energy-related pollutants. Future emphasis will be placed on determining the structure of biomolecules such as DNA and proteins, studying the change in their structure due to interaction with radiation or chemicals, and ultimately relating these changes to the biological activity.

4. Instrumentation Research

The main objective of this program is to develop state-of-the-art instrument and measurement technology and methodology for use in detecting and studying the consequences of energy-related pollutants such as radiation and chemicals on the environment and health. The program emphasizes development of the technology of radiation detectors to better characterize radiation sources, enable more accurate and precise measurements of exposure to all forms of ionizing radiation, and provide more reliable and scientifically defensible estimates of radiation doses. The natural radiation background and physical mechanisms of radiation transport are also studied. These studies are important, for example, in understanding the transport and behavior of radon in the indoor environment and determining the exposure from radon and its progeny. Quality control and assessment of radon dosimetry and personal dosimetry are conducted under this program. In the future, emphasis

will be placed on accurate determination of dose in mixed radiation fields consisting of x rays and neutrons.

Another focus of this program is on research that will contribute to structural biology studies using synchrotron x-ray sources and to medical applications of nuclear technology. Instrumentation and techniques are being developed with emphasis on extremely sensitive methodologies capable of measuring biological damage at the cellular and subcellular level.

B. Biotechnology

The importance of biotechnology to the health of the Nation's industrial and scientific base is being increasingly recognized as these technologies spread from current areas of application in biology, medicine, and the pharmaceutical industry to sectors including energy (biomass production), environment (bioremediation of waste), agriculture, materials science, and chemical engineering, including biomaterials and engineered enzymes for biocatalysts. The Biomedical and Environmental Research Program, which is providing the scientific focus and foundation for DOE's biotechnology activities, also expects to exploit the advances in understanding the structure, organization, and function of genetic structures for assessing the human risk from radiation and other environmental factors. New technologies developing at the boundaries between nuclear medicine, instrumentation development, and molecular biology are fostering the development of a new generation of medical applications for the study, diagnosis, and treatment of human diseases.

1. Human Genome

The Human Genome Program is aimed to reach Departmental goals, among them, the promise of many new opportunities and breakthroughs in biotechnology, e.g., the improvement of human lives through the development of new products, pharmaceuticals, and therapies for a multitude of human diseases. Further expected benefits will include improved risk assessments for individuals and populations exposed to agents that have an impact on genetic materials and applications to environmental and remediation issues.

The DOE Human Genome Program stresses mapping; the development of sequencing technologies and instrumentation; and the development of approaches to the storage, query, and manipulation of the vast amount of genetic and sequence data that the program will yield. The program also emphasizes studies on the ethical, legal, and social issues arising from the program, particularly in the area of privacy and confidentiality of genetic information. Crosscutting through these goals is the very important, Department-wide imperative to foster and promote science education activities; for this, the multidisciplinary Human Genome Program is ideal because it brings together so many disparate disciplines, technologies, and sciences.

The abstracts in this publication cover research highlights from the program as a whole and from the three principal Human Genome Centers at the Lawrence Livermore, Lawrence Berkeley (LBL), and Los Alamos National Laboratories. These national laboratory facilities have been especially successful because they are organized to foster interdisciplinary projects and to use advanced technologies, although originally built for other purposes, to help advance the goals of the Human Genome Project. In the areas of advanced instrumentation and informatics, progress has been rapid.

In the area of map construction, researchers at Lawrence Livermore National Laboratory's Human Genome Center have essentially finished (more than 90 percent completed) the physical map of chromosome 19. They have prepared "finger-printed" clones, each element of which is uniquely identified and most of which have been ordered along the length of chromosome 19. At Los Alamos National Laboratory's Human Genome Center, researchers have achieved similar coverage of chromosome 16. These resources have already proved valuable for localizing several disease genes, among them the myotonic dystrophy gene on chromosome 19q13.3 and the Batten Disease gene on the p arm of chromosome 16. Work supported by a DOE grant to the Baylor College of Medicine has recently resulted in the identification of the Fragile X locus (on the X chromosome). This locus is associated with a form of mental retardation and appears to work through the excess repetition of a three-base sequence near the gene. To facilitate mapping, several resources have been developed by DOE researchers, including "libraries" (arrays of ordered chromosome-specific clone sets), flow-sorted yeast artificial chromosomes, libraries of microdissected chromosome fragments, fluorescence in situ hybridization technology, and robotic instrumentation to manage and manipulate these resources.

In the area of sequencing technologies, multiple approaches continue to be pursued. Among them are sequencing by hybridization (which reconstructs DNA sequence from reactions with known, short oligonucleotide probes), and extensions of the primer walking technique exploiting a new way of building the 18-base primer required to initiate the synthesis reaction, various approaches for speeding up the critical sequencing gel electrophoresis step with thin or capillary gels. Additional approaches include single molecule sequencing with detection by laser-induced fluorescence and rapid analysis of DNA sequences with mass spectrometry. Finally, about 450 Kb of finished human T cell receptor DNA sequence has been obtained by one DOE researcher.

In the critically important area of computational support (informatics) for the Human Genome Project, continuing efforts on chromosome map assembly, database development, sequence analysis, and laboratory automation are resulting in rapid progress. DOE supports the Genome Database at Johns Hopkins University, which is the primary community database for human chromosomal mapping data; this resource is available to any researcher in the world connected to the Internet. DOE sponsored

scientists continue to contribute to the DNA sequence database GenBank, first built at the Los Alamos National Laboratory and now managed by the National Library of Medicine. Sequence analysis software is an emphasis of the DOE Human Genome Program. Laboratory automation is advancing, making obtaining research data easier and more efficient.

A last emphasis of the DOE Genome Program is ethical, legal, and social issues (ELSI) associated with new genetic information that will emerge about individuals. DOE has two major emphases: studies in the area of privacy and confidentiality of genetic information and enhanced public education (including targeted communities) about genetics. ELSI activities include research, reports, educational materials, and conferences.

2. Structural Biology

The mission of the Structural Biology Program is to develop the concepts and tools necessary to achieve a fundamental understanding of macromolecular structure/function relationships. This understanding requires basic research into physical principles capable of providing new means of elucidating complicated structures. It also requires research and development activities directed at creating centers for applying the new principles at major DOE national user facilities in a way that meets the specific needs of biological researchers. Finally, it requires providing the fundamental knowledge, techniques, and tools needed for addressing several major mission areas of the Department, particularly those involving biotechnology (e.g., enzyme catalysis and production of energy from biomass).

Structural biology is an enabling science or technology that provides the foundation for future development of modern biology and biotechnology. Because of its role as custodian of national user facilities for determining the structure of biological macromolecules, the Department has unique responsibilities and opportunities in fostering the development of structural biology. The Department's existing and planned capital-intensive user facilities are a critical element in efforts to achieve fundamental understanding of the relationships between macromolecular structure and function. Hence, these facilities are a critical ingredient in this Nation's biotechnology future. Fundamental understanding of macromolecular structure/function relationships is the key to achieving major national goals in biotechnology and economic competitiveness. It is an essential element in accomplishing departmental objectives in the areas of energy supply, environmental management, and health research.

The principal objectives of the *facility* program in structural biology are to—

- Upgrade staffing and resources such as laboratory space at existing light sources so that they can provide satisfactory service to the national biology user community (academic and industry).

- Design and construct biology user stations at the new DOE light sources (the Advanced Light Source at LBL and the Advanced Photon Source at Argonne National Laboratory).
- Develop upgraded and new biology user stations at DOE neutron facilities, to provide access to neutron technologies for structural analysis to the national biology user community.

The abstracts include listings of structural biology user stations at, for example, the National Synchrotron Light Source, the High Flux Beam Reactor, the High Flux Isotope Reactor, and the Stanford Synchrotron Radiation Laboratory.

The principal objectives of the *research and training* program in structural biology are to—

- Support research leading to timely development of critical technologies and infrastructure, such as detectors and computational algorithms, for biology stations at the DOE national user facilities.
- Support selected research projects designed to demonstrate the potential of structural biology and of the major user facilities for contributing to the solution of major problems in biology.
- Train scientists in the techniques of structural biology.

Several projects, for example, are directed at providing state-of-the-art semiconductor device detectors for x rays such as charge-coupled devices.

3. Medical Applications

The broad objective of the Medical Applications Research Program is to improve current diagnostic and therapeutic capability. The thrust is to demonstrate clinical feasibility through research on radioisotope development, radiopharmaceutical chemistry, advanced imaging instrumentation, innovative radiation therapy, and a new initiative: molecular nuclear medicine. DOE's role is to carry a new technology to the point where clinical feasibility has been demonstrated. Researchers would then look to the National Institutes of Health (NIH) to support a clinical efficacy study, if such were necessary, involving, for example, a randomized clinical trial; researchers would talk to industry representatives to market improved instrumentation.

Research with accelerator and reactor-produced radioisotopes is conducted to develop new nuclides with improved imaging properties, higher specific activity, enhanced purity, etc. The thrust in radiopharmaceutical chemistry research is to develop improved compounds for localization in tumors in order to enhance early cancer diagnosis and to achieve advancements in radiopharmaceutical therapy. Improved radiolabeled compounds also are used to study normal and abnormal organ functioning, which is also aimed at improving early diagnosis of diseased states as well as providing new insights into organ

physiology. The thrust of the instrumentation development effort is to improve spatial resolution and sensitivity of imaging devices and to enhance algorithms for data analysis and display. Novel approaches such as magnetoencephalography may enable completely new insights to be gained into brain functioning and provide a radically different methodology for detecting brain disorders. Innovative radiation therapy technology is pursued such as boron neutron capture therapy, photoactivation therapy, photodynamic therapy, and other promising approaches.

The Medical Applications Research Program integrates expertise in medicine, physics, chemistry, engineering, and computer science to enable a multidisciplinary effort to advance clinical medicine. The scope of the program ranges from initial in vitro and experimental animal studies to limited investigations with human subjects. Close interface is maintained with NIH, particularly as research approaches the large scale clinical investigation phase.

Efforts are in progress to develop a new research area, Molecular Nuclear Medicine, by exploiting the opportunities presented by the revolution in the biological sciences. The strategy is to integrate the scientific and technical power of molecular biology with the existing nuclear medicine program. Research in molecular biology has provided significant insight into the mechanisms of macromolecular interactions underlying normal genetic, cellular, and physiological processes that when disrupted can lead to pathological states and diseases. Molecular technologies, when coupled with the range of instrumentation and techniques of nuclear medicine, have the potential to provide tools of much higher sensitivity and precision for detecting, localizing, and potentially for ameliorating, macromolecular, cellular, and systemic pathologies.

II. ENVIRONMENTAL RESEARCH

A. Environmental Processes and Effects

The objectives of the Department's Environmental Processes and Effects Research (EPER) Program are to (1) quantify the physical, chemical, geological, and biological processes that transport, disperse, and transform energy-related materials in the atmosphere and through terrestrial and marine ecosystems; (2) determine the mechanisms of degradation and detoxification of hazardous energy-related materials in the environment; and (3) determine and manage the capacity for ecosystem adjustments to energy-related environmental stresses. In pursuing these objectives, EPER research helps develop the scientific tools to assess the environmental consequences of energy-related activities and to promote improvements in environmental quality. EPER currently includes four components which focus on local and regional environmental problems of concern to DOE:

1. Atmospheric Chemistry and Dynamics

The Atmospheric Science Program develops a comprehensive understanding of the atmospheric processes that control the transport, transformation, and fate of energy-related air pollutants. The objectives of the research in progress are to—

- Understand the atmospheric chemistry processes of energy-related air pollutants (e.g., sulfur and nitrogen oxides, ozone, etc.) in both gas and aqueous phases, their gas-to-particle conversion and fate, including deposition and resuspension.
- Understand the meteorological processes that control the dispersion of material releases to the atmosphere over complex terrain, e.g., in mountainous regions.
- Develop the predictive models of the previously mentioned processes and acquire the data to validate them.

2. Ocean Margins

The Ocean Margins Program addresses a quantitative understanding of the dispersal and fate of energy-related materials at the land/ocean interface. The principal focus of this program is on the fluxes of carbon in the coastal ocean and its implications to the global carbon cycle and therefore to global climate change. The objectives of the research in progress are to—

- Quantify the fluxes, exchange, and fate of carbon and other biologically important elements or energy-related materials along the ocean margin and define ocean-margin sources and sinks in global biogeochemical cycles.
- Determine the mechanisms underlying these fluxes and the frequencies over which they operate.
- Determine the mechanisms by which dissolved organic carbon, particulate organic carbon, and dissolved inorganic carbon are converted by molecular and microbial processes in coastal waters and sediments.

3. Subsurface Sciences and Environmental Radon

The Subsurface Science Program emphasizes long-term mechanistic research within the subsurface biosphere. It contributes to resolving problems of (1) contaminant transport that result from surface and shallow land burial of defense- and energy-related wastes and (2) environmental restoration at DOE sites. The principal objectives of the research in progress are to—

- Develop a mechanistic understanding of and improved prediction of subsurface (subsoil/groundwater) processes, including organic/radionuclide mobility and stabilization using chemical and biotechnological methods.
- Characterize microbial communities at depth, using new and advanced physical, computational, and biotechnological approaches. Microbial genesis, the origins of the communities, will also be a focus of this research.

- Evaluate the long-term effects of contaminants and remedial actions on natural subsurface systems, emphasizing microbial ecosystems.
- Facilitate the transfer of technology to DOE sites, DOE Office of Waste Management, and industry.

The Environmental Radon Program encompasses basic research on the sources and transport of radon in the environment and on processes that affect its entry into buildings. The objectives are to—

- Define the availability and emanation potential of radon within the geological environment and identify areas with potentially high indoor radon concentrations.
- Quantify the environmental mechanisms that control radon transport.
- Develop models linking radon availability and transport in soils to its entry in buildings.

4. Ecological Research

The objectives of these research programs were to define and model energy and material transport within ecological systems.

These objectives and related research programs have since been reorganized into a program focused on ecological adjustment to environmental variations and changes, the Program for Ecosystem Research (PER).

The PER examines the processes of ecosystem adjustment to environmental changes that are useful in restoring and protecting ecosystems adversely effected by energy-related environmental actions. The objectives of the research in progress are to—

- Determine how ecosystems adjust to environmental variations and changes.
- Resolve how organismic responses during the ecosystem adjustments are controlled.
- Develop methods that can be used to quantitatively integrate responses and their controls across temporal and spatial scales.

B. Global Change

The objectives of the Global Change Research Program are—

- To predict the future atmospheric concentrations of carbon dioxide and other energy-related greenhouse gases.
- To predict the rate and magnitude of potential climate change due to the enhanced greenhouse effect.
- To understand both the direct impacts of greenhouse gas emissions on biota (e.g., effects of carbon dioxide enrichment) and the indirect consequences due to climate change.

This information is necessary for assessing the economic and environmental costs and benefits of both potential climate change due to the effects of greenhouse gases and implementing different technologies and energy policy options aimed at preventing, mitigating, or adapting to such change. The research described can be broadly categorized into seven areas:

1. Climate Modeling

Climate defines the physical environment to which humans and the biosphere respond. The principal components of the climate system are the atmosphere, the oceans, the cryosphere, and the land surface. As carbon dioxide increases in the atmosphere, the climate will respond (e.g., atmospheric energy balance is modified with temperature expected to increase; and ocean physical and chemical characteristics are expected to change). The many complex interactions within the climate system, called *feedbacks*, will further modify the response. For example, changes in cloudiness may either enhance or reduce a greenhouse warming. This is called *cloud feedback*. The general circulation models (GCMs) are presently incapable of realistically treating the clouds or oceans. Model improvement, data collection, and analysis will be required.

The research objectives for the funded research are—

- To develop and improve the capabilities to estimate the range of global and regional climate change resulting from increasing carbon dioxide.
- To detect evidence of the climate response to the past and continuing increase in atmospheric carbon dioxide.
- To provide information needed for resource analysis, such as regional rate and magnitude of changes in temperature, precipitation, soil moisture, and extreme events.

2. Computer Hardware, Advanced Mathematics, and Model Physics

Predicting the future climate response will require climate models capable of much longer and more numerous simulations, finer resolution, and significantly improved representation of the physics and chemistry of the climate system than presently available. Climate models with such capabilities will require computers capable of increasing throughput by a factor of at least 10^4 over that obtainable in 1990, mathematical formulations and software that utilize the extensive parallelism of the emerging generations of computers, and improved algorithms that have been more thoroughly verified using more comprehensive sets of field observations.

The Computer Hardware, Advanced Mathematics, and Model Physics (CHAMMP) Program will develop coupled climate system models employing the hardware and software capabilities offered by emerging computer architectures to address the challenging physics of understanding the climate system. The objectives of the funded CHAMMP research projects are—

- Near term (1990-1992): Achieve improved performance of existing climate system models by taking advantage of emerging parallel computing architectures.
- Intermediate term (1992-1995): Design and develop scaleable submodels of climate system components capable of achieving in excess of 100 Giga FLOP (billion floating point operations per second) performance.
- Extended term (1995-2000): Improve and assess the initial versions of the next-generation climate system submodel components, assemble an optimized model, and execute scientifically valid simulations for long-term climate predictions with 10 TeraFLOP (trillion floating point operations per second) performance.

The CHAMMP initiative is designed to bring study of the climate system to the forefront of scientific problems taking advantage of the developing computational capabilities underway as part of the Federal High Performance Computing and Communications Program.

3. Quantitative Links

The *sense* of science is that greenhouse gases can theoretically cause warming, but the *state* of science is one of incomplete model prediction and inconsistent observations. An urgent need exists for unequivocal detection of climate change, including greenhouse warming. Unambiguous data and scientifically valid approaches do not now exist. The Quantitative Links Research Program seeks to resolve this problem. Its objectives are to establish the relationships between and the processes controlling—

- Changes in atmospheric composition (particularly carbon dioxide).
- Changes in radiative fluxes.
- Changes in local temperature and long-term changes in global temperature (or other global changes in climate that may result from changes in atmospheric composition).

A broad range of research on the linkages between changes in atmospheric composition and global change is conducted to address these objectives. Measurements (field and laboratory) to quantify the relationships are the primary focus.

4. Atmospheric Radiation Measurement Program

The Atmospheric Radiation Measurement (ARM) Program is the feature component of the Department's research strategy to address global climate change. The ARM Program is a highly focused observational and analytical research effort that will compare observations with model calculations in the interest of accelerating improvements in both observational methodology and GCMs.

The ARM Clouds and Radiation Testbed (CART) facilities include—

- A southern great plains (U.S.) site, which is already operational.
- A tropical western Pacific Ocean site scheduled for operations in 1993 to 1994.
- A north slope of Alaska site scheduled to begin operations in 1995.
- Two additional climatologically important locales have been identified for consideration.

Data for the general science community will be made available through a data archive being established at Oak Ridge National Laboratory.

The research objectives for the program and funded research are—

- To describe quantitatively the radiation balance from the surface to the top of the atmosphere.
- To determine the atmospheric characteristics responsible for this balance.
- To improve the parameterization of the formation and evolution of clouds in climate models, to create an experimental testbed for testing process models used in GCMs and for the support of satellite ground truth measurements.

5. Global Carbon Cycle and Vegetation Research

The Global Carbon Cycle Research Program provides the scientific underpinnings for predicting future concentrations of carbon dioxide in the atmosphere. The research addresses natural systems that govern abundance of carbon dioxide in the atmosphere, including the role of oceans and terrestrial ecosystems in determining exchanges of carbon dioxide with the atmosphere. In addition, carbon cycle research compiles information about technology, economics, geology, and other factors required for estimating emissions of carbon dioxide.

The current program is designed to take the next step beyond the current inventory of knowledge of the carbon cycle. It aims to increase knowledge and understanding of terrestrial components of the global carbon cycle in order to predict more accurately change of atmospheric carbon dioxide from energy emissions. Specific objectives for the funded research are—

- To understand processes controlling exchange rate of carbon dioxide between atmosphere and terrestrial biosphere.
- To document energy emissions of carbon dioxide.
- To evaluate source sink mechanisms for atmospheric carbon dioxide.

- To develop reliable models for projecting atmospheric concentrations of carbon dioxide.
- To develop the scientific, technological, economic, and geologic data needed for estimating emissions of carbon dioxide from energy activities.

The Vegetation Research Program provides information about (1) the effects of carbon dioxide and climate on plants and the vegetative component of ecosystems and (2) plant physiological controls that affect exchange of carbon dioxide between the atmosphere and terrestrial biota. The research strategy is to determine primary effects of increasing carbon dioxide and temperature/moisture stress for representative plants and to develop modeling approaches for extrapolating basic information on processes and controls to other plant and ecological systems. A key facet of the research is to acquire new experimental data and develop and validate models for understanding effects of altered carbon dioxide and climate conditions on plants and ecosystems. The research objectives of the funded research are—

- To understand plant physiological mechanisms that control carbon dioxide fixation, and the net carbon dioxide uptake by plants of terrestrial ecosystems; this involves experiments to determine the role of plants and terrestrial ecosystems as sinks in the global carbon balance.
- To experimentally determine relative effects of increased carbon dioxide and altered climate conditions on representative plants and ecosystems.
- To develop models for predicting effects of changing carbon dioxide and climate on vegetation.

6. Oceans Research

The oceans have an important role in the Earth's climate system and in determining the fate of natural and anthropogenic carbon dioxide in the atmosphere. For example, the oceans are the largest known sink for anthropogenic carbon dioxide. The oceans also could delay detection of increased surface air temperature resulting from carbon dioxide emissions by storing excess heat. Uncertainties about complex interactions among oceanic heat and carbon storage and apparent imbalances between sources and sinks of carbon underscore the need for focused ocean research to accomplish the core goals of the global carbon and climate research programs. Oceans research has developed a comprehensive approach that involves laboratory and field measurements, advanced models, new instrumentation, and remote sensing techniques to provide critical scientific information. The objectives of the funded research are—

- To improve the treatment of physical processes in ocean models to be used for the prediction of climate at regional scales.
- To develop a global data set describing the oceanic carbonate system for the calibration and verification of ocean

carbon cycle models, in cooperation with the World Ocean Circulation Experiment and the Joint Global Ocean Flux Study.

7. National Institute for Global Environmental Change

The National Institute for Global Environmental Change (NIGEC) was established by Congress in 1989. The purpose was to plan jointly with DOE and to conduct through Regional Centers a balanced research program relevant to DOE's Global Change Research Program. The Institute is to support research that serves the following needs—

- Improves scientific understanding of the mechanisms of global climate change.
- Reduces key scientific uncertainties surrounding sources and sinks of energy-related greenhouse gases and aerosols.
- Improves assessments of the potential impact of atmospheric and regional climatic changes due to the buildup of aerosols and greenhouse gases in the atmosphere.

- Reduces key scientific uncertainties inherent in the projections of future climate states and the perturbations attributed to human activities.
- Develops methods and approaches for assessing the economic costs and benefits of human-induced climate change and the costs of policy options applicable to preparing for plausible climate change.

NIGEC also is to provide education and training opportunities to increase the flow of talented young researchers into global environmental change research areas. NIGEC has adopted the following balance to its academic research program: research on the scientific aspects of global environmental change (75 percent), research undergirding the socioeconomic analysis of policy strategies and options related to global climate change (20 percent), and educational efforts (5 percent).

Research Profiles of Major OHER-Supported Programs at DOE Facilities

DOE laboratories are of two types: nine large multiprogram facilities, which conduct work in several areas of technology for different organizational components of DOE, and about 30 specialized laboratories, each primarily dedicated to conducting the research for one of the Department's program offices. Both kinds of facilities serve as national resources, performing research for other Government agencies and the private sector, while often making available their unique physical resources and capabilities to university and industry investigators for their own use or for collaborative research. The laboratories also cooperate in the education of scientists, including students, postdoctorates, visiting staff, and faculty, by offering special training and research opportunities in the various resident disciplines. Profiles of the research underway for the larger DOE laboratory efforts supported by OHER are presented in this section to provide both a perspective of their respective roles in the Department's Biomedical and Environmental Research (BER) Program and to help those interested in exploring opportunities for developing a professional relationship at the laboratory. Further inquiries may be directed to the coordinator listed for each facility or to the individual investigator whose research is abstracted in the subsequent sections.

The funding amounts cited for each laboratory represent expenditures for FY 1992 and are provided only as an indication of the relative size of the BER programs at each institution.

MULTIPROGRAM LABORATORIES

Argonne National Laboratory

FY 1992 Budget: \$11.6 Million

Research sponsored by DOE, Office of Health and Environmental Research (OHER) at Argonne National Laboratory is conducted primarily in the Biological and Medical Research Division and the Environmental Research Division, with some effort in nuclear medicine in the Chemistry Division.

Many of the studies are aimed at defining the biological and medical hazards to humans from energy technologies and new energy sources. These investigations have a strong base in fundamental research in a variety of areas, including molecular physics and chemistry, biophysics, molecular and cellular biology, radiobiology, occupational and environmental health, and environmental science.

Staff in a fundamental molecular physics and chemistry program conduct basic research on atomic and molecular interactions. Results from this research are used to model initial stages of radiation effects in matter, to facilitate advances in measurement sciences, and to help elucidate basic atmospheric processes. Examples of current work include use of—

- Resonance-enhanced multiphoton ionization (REMPI) to explore the physics and chemistry of excited states of atoms and molecules.
- REMPI to study free radicals, clusters, and other reactive or trace species; vacuum ultraviolet photo-ionization studies that make use of synchrotron radiation as well as laboratory continua in combination with photoelectron, ion, and fluorescence analysis.
- Various electron impact studies of atoms and molecules, including electron energy loss, differential scattering, and fluorescence detection schemes.
- Theoretical radiation physics studies related to the interaction of photons, electrons, and other charged particles with matter.

Research in biophysics focuses primarily on elucidating the molecular structure of biologically significant molecules and coordinating structure with function through crystallographic, chromatographic, site-specific mutagenesis, and computer modeling techniques. The molecules under study include antibodies, toxins, enzymes, and the photosynthetic reaction center. The structural properties of the reaction center as determined crystallographically are correlated with its spectroscopic properties through collaboration with scientists in the Chemistry Division, site-directed mutagenesis of the reaction center and subsequent crystallographic and spectroscopic examination provide further information. Protein-protein and DNA-protein interactions are studied by a quantitative gel-infiltration technique.

Research in molecular and cellular biology encompasses a wide variety of studies focused on explaining the genetic and biochemical mechanisms underlying human health problems, including carcinogenesis. Gene expression and cell differentiation are studied in cultured human and rodent cells exposed to chemicals that modulate the carcinogenic process; carcinogen-induced genetic damage is investigated through the use of defined genetic targets constructed by recombinant DNA tech-

niques. Experiments at the tissue and whole-animal levels are designed to elucidate the mechanisms of multistage tumorigenesis and the nature of the gene-control processes that are functionally linked to the expression of neoplasia. Alterations in tissue protein expression as a result of chemical or radiation exposure are also being studied. Part of the Human Genome Program is represented by a project aimed at large improvements in the speed of DNA sequencing. The technique of sequencing by hybridization involves the development of a production-line system for hybridizing DNA with oligonucleotides and computerization of the data analysis from such experiments. Other biological studies focus on the toxic effects of cadmium and lead, which are metals of concern in occupational exposure.

Radiobiological research includes a variety of studies that focus on the development of a unifying concept of radiation damage and the provision of information that will facilitate the prediction of human health risks. Studies include molecular biological investigations of gene induction in response to various qualities, doses, and dose rates of radiation; in vivo and in vitro analyses of radiation effects on hematopoietic systems. Studies also include assessments of various types of cultured mammalian cells of the transformational, cell-killing, and mutational effects of various radiations. Inhibitors, promoters, and radioprotective compounds are used as a means of identifying specific lesions induced by radiation, as well as the means of their repair. Statistical studies of radiation exposure and carcinogenesis are being conducted, aimed at the prediction of risk across species lines.

A major component of research in occupational and environmental health involves an assessment of the levels and effects of alpha-particle-emitting radionuclides in humans. Other studies are focused on an examination of specimens to determine the expression of specific oncogenes. Included is an ongoing study of the late effects of radium in persons exposed either occupationally or medically.

Research conducted within the Environmental Research Division is directed to the study of effects of biologically important pollutants and byproducts released to the environment by various energy technologies. These investigations have a strong base in a variety of scientific disciplines including chemistry, terrestrial ecology, and meteorology.

Atmospheric research is conducted on the transport, diffusion, chemical transformation, and deposition of airborne trace substances. Experimental techniques include ground-based remote sensing and use of in situ sensors on tethered balloons and towers. The structure of the atmospheric boundary layer is studied with acoustic remote probing methods, and air-surface exchange of trace substances is measured with micrometeorological techniques. Theoretical and numerical modeling methods are used to interpret and extend the results. In atmospheric organic chemistry, investigators use laboratory, field, and mod-

eling techniques to evaluate the importance of organic compounds and greenhouse gases in global tropospheric issues.

Atmospheric research, in support of a major DOE program on global climate, is also conducted on the physical processes of the atmosphere that affect the global solar and infrared research budget. Experimental techniques emphasize ground-based remote sensing, and numerical modeling efforts center on cloud microphysical processes, aerosol behavior, and radiation exchange.

Research on environmental effects includes a study of the contribution of biotic factors to the formation of soil structure and the associated pore space. This research uses the chronosequence of tallgrass prairie reconstructions at the Fermilab Research Park to investigate the ways plants, their mycorrhizal fungi, and the associated soil biota respond to or influence the nutrient cycles initiated by soil aggregation. Other studies use field, laboratory, and modeling techniques to investigate the effects of various burn and fertilizer regimes on aboveground and belowground production.

In studies of interactions between climate and vegetation, the responses of trees to climate-related stress are being characterized, and the carbon cycle over the last two glacial periods is being examined through modeling and statistical approaches.

Research has been initiated to determine the chemical interactions occurring in mixed-waste contaminated subsurface groundwaters. These studies are part of OHER's Subsurface Science Program. State-of-the-art spectroscopies, particularly Fourier transform, laser Raman, and infrared, are being used to determine the chemical binding in solution and rock matrices of contaminants. Radiochemical trace methods are being used to determine the quantitative interactions.

The Nuclear Medicine Research Program in the Chemistry Division at Argonne involves two major areas of research. One is the development of radiopharmaceuticals for both diagnostic and therapeutic purposes. These agents include compounds developed for imaging tumors, therapy for gynecologic tumors, and therapy using monoclonal antibodies. This effort includes the production of the radionuclides, the synthesis of precursor compounds, the radiolabeling of the compounds, and preclinical testing. The second research area involves the biologic effects of the therapeutic agents developed in the program. These investigations include the effect of the different forms of radiation on a macroscopic, cellular, chromosomal, genetic, and molecular level. This research also examines the use of radiosensitizers and radioprotectors to modify the toxicity of the radiation in order to maximize the effect on target tissue. Clinical studies of these agents are undertaken in collaboration with medical researchers around the country.

The specialized facilities available for biological research include an accredited animal facility; a broad spectrum of radiation sources that includes gamma, x-ray, ultraviolet, and

visible light radiation facilities; specialized whole-body counting facilities for human radiobiological studies; carcinogen and cytofluorographic laboratories; specialized two-dimensional protein electrophoresis and x-ray crystallography laboratories and an excellent laboratory for laser photophysics of atomic and molecular species; and a state-of-the-art meteorological tower for onsite atmospheric studies.

The professional staff supported by OHER consists of 54 scientists (30 are in Biology and Medicine, 21 in Environmental Research, and 3 in Chemistry), 35 of whom have Ph.D.s in specialties ranging from cell biology, computer science, and chemistry, to physics, mathematics, and meteorology. In addition, OHER supports 12 postdoctoral fellows who are currently in residence. Work for others is funded at a level of \$14 million, supporting some 40 scientific staff, 30 in Environmental Research, and 10 in Biology and Medicine.

Current OHER-funded collaborative efforts are underway with Brookhaven, Oak Ridge, and Pacific Northwest Laboratories and the National Institute of Standards and Technology. In addition, a collaboration with a host of academic institutions includes the University of Chicago, Yale, CalTech, and the University of Notre Dame.

Technology transfer is primarily in the areas of pharmaceuticals (characterization), techniques for groundwater purification, soil remediation, and quantification, in various media, of toxic elements, including cadmium, lead, and zinc.

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Brookhaven National Laboratory

FY 1992 Budget: \$24.9 Million

Brookhaven is a multidisciplinary laboratory whose efforts in Biological and Environmental Research (BER) span the world, the human body, animals, cells, viruses, and molecules. Its strong basic and applied programs—characterized by many collaborations within the laboratory, with faculty and students from universities, and investigators from industry and other national laboratories—build upon the laboratory's unique and specialized facilities and the expertise of its internationally recognized scientific staff. The unique and specialized facilities, all of which are operating, include: (1) the High Flux Beam Reactor (HFBR), (2) the National Synchrotron Light Source (NSLS), (3) scanning transmission electron microscopes (STEMs), (4) the Protein Data Bank, (5) the Brookhaven Linear Isotope Producer (BLIP), (6) the Brookhaven Medical Research Reactor (BMRR), (7) positron emission tomography (PET) scanners and two cyclotrons and associated laboratories devoted to the production of short-lived radiopharmaceuticals, (8) single-photon emission computerized tomography (SPECT) scanners, (9) a whole-body counter for body composition studies, (10) an accredited Ambulatory Clinical Research Facility, (11) a state-of-the-art Radiation Therapy Facility, (12) an accredited Animal Facility, (13) a state-of-the-art Inhalation Toxicology Facility, and (14) Free-Air Carbon Dioxide Enrichment Facilities for assessing the effects of changes in carbon dioxide concentration on crop plants in the field.

Some of the facilities are used for many different types of investigations. For example, the x-ray ring of NSLS is used to measure x-ray scattering and x-ray diffraction of biological samples in very short times, making it possible to analyze smaller samples and crystals with less radiation damage, and hence, higher resolution. NSLS is also being used for preliminary clinical trials of noninvasive coronary angiography, a beamline is being adapted for the scanning of head and neck to detect calcium distribution, and, by use of two wavelengths, the integrity of arterial blood flow and the intense photon beams are being used for microplanar tumor therapy.

The BER programs are conducted in the Departments of Applied Science, Biology, Chemistry, and in the Medical Department. Areas of basic research in the Biology and Medical Departments include (1) studies of replication, transcription, and translation in animal and bacterial virus systems; (2) studies on recombination, repair, and genetic transformation in bacterial systems; (3) mechanisms by which chemicals and radiation kill or transform mammalian cells, DNA repair in mammalian cells, and the means by which such parameters vary in the human population; (4) cytogenetic studies on normal human cells and on cells sensitive to particular chemical or radiation treatments so as to detect a sensitive subset in the human population; (5) molecular studies on the sequence, structure, and function of proteins including proteases and their role in tissue remodeling and metastases; and (6) a program in genome

research which is oriented primarily toward developing technology for large-scale DNA sequencing analysis.

BNL has active and expanding programs in DNA sequencing and structural biology. The former builds upon a breakthrough in DNA sequencing by primer walking with strings of contiguous hexamers, which should lead to automated sequencing of cosmid DNAs. The latter exploits a complex set of instruments at NSLS, HFBR, and the STEM Facility. The Biology Department operates stations at NSLS for monochromatic and Laue x-ray crystallography, time-resolved small-angle x-ray scattering, and ultraviolet spectroscopy. Stations at HFBR allow small-angle neutron scattering, membrane diffraction, and neutron crystallography. STEM is capable of direct mass measurements on unstained proteins and nucleic acids, a CryoEM for high resolution analysis of frozen hydrated specimens is soon to be operating, and a third STEM will identify atomic composition by energy-loss spectroscopy.

In-house research drives the development and improvement of these facilities, which are operated for the benefit of the structural biology community at large. Examples of work being done at BNL using these facilities include analyzing the structure of chromatin, ribosomes, and viruses; crystallography of biologically interesting proteins such as histones, ribosomal proteins, T7 lysozyme, and a DNA methylase; repressor-inducer interactions; changes in atomic positions during protease action; locations of hydrogens and water molecules in protein structures; conformational changes upon activation of tissue plasminogen activator; and protein-nucleic interactions involved in transcription and replication.

In the Medical Department, extensive research includes (1) total body composition and trace metal studies using unique whole-body neutron activation and counting facilities; (2) production of isotopes in BLIP and HFBR for diagnostic and therapeutic purposes; (3) development of new instrumentation and methods, including SPECT, for measuring regional and global distribution, clearance, and metabolism of radiopharmaceuticals including radiolabeled monoclonal antibodies; (4) targeting of stable and radioactive isotopes to tumors for radiotherapy (an important aspect of this work is the use of ^{10}B for neutron treatment of brain tumors and malignant melanoma using the epithermal neutrons from BMRR); (5) development of microplanar therapy using intense x-ray beams from NSLS; and (6) Chemistry and Medical Department's nuclear medicine, including high resolution whole body PET, using a number of short-lived, positron-emitting isotopes to label biological substrates to study such diverse brain problems as (1) brain energy metabolism as it is affected by schizophrenia, Alzheimer's disease, stroke, drugs, alcohol abuse, etc.; (2) human cerebral malignancy by assessing brain metabolism with particular radiotagged molecules so as to monitor the degree of malignancy and response to therapy; (3) functional enzyme activity using inhibitors and labeled drugs; and (4) therapeutic drugs and their target receptors, their pharmacokinetic characteristics, and the permeability of the blood-brain barrier. Other

specialized facilities available for the above research include (1) two cyclotrons for radionuclide production, especially short-lived positron emitters; (2) PETs for noninvasive measurements in animals and humans; and (3) large animal facilities including a primate colony dedicated to PET research.

In the environmental field, extensive programs in the Department of Applied Science study problems arising from energy-related emissions to the atmosphere and to the surface and subsurface layers in (1) the development of instrumentation and tracers for continuous monitoring of ground level and airborne emissions; (2) the atmospheric chemistry and physics of organic pollutants; (3) the modeling of meteorological processes; (4) the cycling of natural and energy-related materials in subsurface environments and how they are affected by microbial transformations of trace metals and organic compounds; (5) the productivity of the coastal shelf and the pathways and rates of energy and material transfer; and (6) investigations of the biomedical and environmental impacts of energy production and use and health studies relating to synfuels and occupational danger analysis. Fully equipped research vessels are available for oceanographic research, and specially outfitted aircraft are employed for atmospheric sampling.

The Environmental Chemistry Research Program includes work on the atmospheric chemistry of gases and aerosols with particular attention to questions such as acid precipitation, oxidant formation, and organic chemistry in areas of (1) research in atmospheric chemistry including field and laboratory investigations of chemical processes in clouds; (2) studies in thermodynamic, kinetic, and optical properties of atmospheric aerosols; (3) development and application of methods for characterization and determination of low concentrations of atmospheric gases and aerosols; and (4) development and application of methods for use of tracer compounds for characterizing long-range transport and dispersion in the atmosphere and air exchange in buildings.

The staff of 330 in FY 1992 consisted of 128 scientists and engineers, 21 postdoctorates, 101 technical assistants, 49 administrative personnel, and 31 students and visiting scientists. Forty-six percent of the staff are supported by organizations other than DOE.

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Lawrence Berkeley Laboratory

FY 1992 Budget: \$18.5 Million

The Biological and Environmental Research (BER) Program at Lawrence Berkeley Laboratory (LBL) has evolved out of the Donner Laboratory, initially established in the early 1940s to conduct basic research on the dynamics of living cells and the interaction of radiant energy with organic matter. Today, BER's role within LBL is expanding as biotechnology's promise is beginning to be realized in the international industrial arena.

LBL's BER program fuels research in the areas of Life Sciences, Structural Biology, Energy and Environment, Earth Sciences, Engineering, and Information and Computing Sciences. These diverse disciplines combine in an effort to explore and mitigate the long-term health and environmental consequences of energy use and to advance solutions to major medical challenges. BER funding is sustaining the endeavors of 109 researchers, 36 support staff, and 54 visiting scientists, graduate students, and undergraduates.

Environmental Research

LBL features a leading national research effort on the indoor environment. This well-integrated project investigates the physics of radon entry into homes, the physical behavior of radon and its decay products in indoor air, and the consequent exposures. In collaboration with the California Department of Health Services, volatile organic compounds in office buildings are being measured, and new risk assessment methods based on fundamental biological mechanisms are being developed for benzene, a common indoor pollutant. LBL has support from the University of California Tobacco-Related Disease Research Program to investigate environmental tobacco smoke, also a major indoor air pollutant.

Atmospheric aerosol particles may influence global and regional climate directly by scattering and absorption of solar radiation or indirectly by modifying the radiative properties of clouds. Clouds reflecting a larger fraction of the incident solar

radiation into space can cause an atmospheric cooling effect. Results obtained from our field studies are used to design laboratory simulation experiments with the LBL cloud chamber to identify the physics and chemistry of dominant importance in modifying the optical and chemical properties of clouds.

Fundamental knowledge of the chemical processes that occur between radionuclides and synthetic organic chemicals present in DOE waste sites will provide the ability to predict more accurately the processes that control contaminant mobilization and transport in the subsurface environment. This basic research on the effect of natural physical and chemical heterogeneity on microbial populations in the subsurface will bear significantly on future applied remediation strategies.

Health Effects Research

During the last decade, LBL has laid the foundation for designing, in tissue culture dishes, an environment that re-creates a functional tissue—the breast—in order to study carcinogenesis. On route, researchers have demonstrated that by manipulating the microenvironmental conditions in a tissue culture system, the yield of desired proteins can be increased, thus enabling a biotechnology-based method for the synthesis of pharmaceuticals. Also, a new rapid assay to distinguish normal from malignant cells has emerged, leading researchers to study the possible underlying mechanism of this fundamental difference, which may be a function of a tumor suppressor gene. The physical events of radiation-induced DNA damage are also under scrutiny, using theoretical modeling techniques based on computer simulation procedures. The National Aeronautics and Space Administration has awarded LBL its Specialized Center for Research and Training in Radiation Health for conducting basic and applied radiobiological research for assessing the radiation risk associated with extended manned space missions.

LBL's expanding hematopoiesis program focuses on the long-term repopulation of stem cells—the cells giving rise to the major components of blood. Our objective is to design stem cell therapy to mitigate the effects of chronic, inherited hematopoietic disorders such as thalassemia.

Structural Biology

LBL's prominent Structural Biology Program integrates the study of molecular complexes and the function of biological molecules from the perspective of their specific three-dimensional structures. The Advanced Light Source, the world's brightest beams of soft x rays and ultraviolet light, will offer dramatic new scientific opportunities for Structural Biology, especially in the fields of x-ray microscopy, spectroscopy, and crystallography. The National Tritium Labeling Facility explores the labeling of compounds to high specific activity with tritium and provides a tritium-labeling service for investigators throughout the country. Structural studies on biologically important molecules are also made possible by new

nuclear magnetic resonance analysis methods. X-Ray Absorption Spectroscopy enables the determination and quantification of intracellular constituents and provides a way to measure the changes induced by drugs and other chemical and physical influences. Other studies are aimed at determining how proteins regulate the expression of genes by examining the structure of the protein-nucleic acid complexes. Structural analyses by electron crystallography help to elucidate the transport of solutes and ions across the cell membrane—a process critical to the biological function of the cell. The new Center for Biomolecular Design will combine the expertise of LBL and the University of California, Berkeley, in the areas of chemical biology and computational biology to analyze and manipulate chemical structure.

The Human Genome Center

The aim of genome research is to make detailed maps and elucidate particular sequences of DNA—the hereditary instructions guiding the development of an organism from conception through senescence. The LBL Human Genome Center excels in genomic DNA sequencing, genetic mapping, physical mapping, and cDNA isolation and analysis. Each of these programs involves close interactions among the biology, instrumentation and automation, and informatics groups. The major biological goal is to assemble physical maps of complete chromosome arms and to develop the capacity to produce genomic sequence of multiple megabases per year. The major instrumentation and informatics goal is to develop the degree of automation needed to produce an effective sequencing assembly line and to capture, assemble, analyze, and distribute massive amounts of sequence information.

Ambitious new bioscience initiatives, complementing the genome project, are emerging at LBL. The Center for Molecular Cytogenetics plays a prominent role in several areas of genetic research, including screening of genetic abnormalities, probe mapping, solid tumor diagnosis and prognosis, and cancer gene localization.

Medical Applications

LBL's Molecular Medicine Program uses both human and transgenic mouse models to focus on atherogenesis, the deposit and degenerative accumulation of lipids on the arterial walls. This program has generated significant scientific breakthroughs and primed potentially lucrative relationships with the biomedical industry. LBL researchers have discovered a gene predisposing individuals to atherosclerosis, the leading cause of heart disease in the country. The National Dairy Board supports the Dairy Research Institute for Genetics and Nutrition at LBL in an effort to explore genetic factors that determine an individual's response to dairy fat and eventual susceptibility to atherosclerosis. This information will then be used to develop improved dietary recommendations for coronary disease prevention.

Traditional nuclear medicine is being revitalized through the use of new chemical probes and new instrumentation for

noninvasive methods of imaging biology function at LBL's Center for Functional Imaging. Positron emission tomography (PET), advanced radiopharmaceutical chemistry, and data analysis join with cell and molecular biology, mathematical modeling, and statistical analysis to address major medical challenges. With the Donner 600-Crystal Positron Tomograph, the distribution of injected radiotracers can be mapped, expediting the development and clinical application of new therapeutic drugs for depression, Alzheimer's, Parkinson's, and other neurological disorders.

An era ended in 1992 with the closure of the last of the particle-treatment facilities at LBL, the Bevalac. A Cooperative Research and Development Agreement is in the works to transfer the proven technology and expertise required for charged-particle radiosurgery to the hospital-based accelerator environment at Loma Linda University Medical Center.

Engineering Resources

The radiation detector and instrumentation program at LBL enables innovative research in low noise electronics, materials science, cryogenics, and mechanical packaging. The laboratory also excels in mass spectrometry, the molecular sizing technology of the future, with respect to large molecules such as proteins and DNA fragments—aiding LBL's genome research. Technology transfer opportunities abound in the area of detector materials and detector instrumentation. A process is being developed to diffuse lithium into silicon for high resolution x-ray detectors generating new opportunities for commercial detector manufacturers to utilize this material.

Education

As a natural outgrowth of the laboratory's affinity with the University of California, LBL has a powerful commitment to improving the Nation's scientific literacy. The Center for Science and Engineering Education promotes equal access to scientific careers for all students and seeks to improve the quality of science and engineering teaching. Summer and academic-term residential programs brought more than 100 students and more than 40 teachers to the laboratory in FY 1992.

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Lawrence Livermore National Laboratory

FY 1992 Budget: \$23.5 Million

Health and environmental research at Lawrence Livermore National Laboratory is celebrating its 30th anniversary this year. The program has grown in breadth since its inception in 1963, when the primary mission was to study the biological and environmental effects of ionizing radiation from nuclear weapons testing. Our goals have broadened considerably in consonance with the changing priorities of DOE. They now encompass the broad aspects of biotechnology research including molecular genetics and genomics, molecular toxicology, instrumentation development, global change, hazardous events and emergency response, and human health and ecological assessments. The current program is organized under two Directorates, the Biology and Biotechnology Research Directorate and the Physical Sciences Directorate. Total staff is composed of 277 professional scientists, 52 support staff, and 32 visiting scientists and students. In addition to Biomedical and Environmental Research (BER) funds, some \$18.5 million is derived from other sources.

Biology and Biotechnology Research Program

The broad mission of the Biology and Biotechnology Research Program is to identify and characterize human health effects from energy use and development. Program goals are to understand the molecular and cellular mechanisms that lead to these adverse effects and to develop technologies and resources to prevent or ameliorate them. This program maps directly onto the long-term goals of the U.S. DOE and OHER, in particular, to provide the scientific foundation for understanding the long-term health consequences of energy use and development and for developing technological solutions for these issues. This is a multidisciplinary, team-research-oriented program and the investigators are adept at coupling scientific strengths in bio-

chemistry, molecular biology, cellular biology, and genetics with the computational, physical, and engineering sciences available from the wider pool of scientists at Lawrence Livermore National Laboratory. The scientific staff is composed of 25 Ph.D.s, 1 M.D., 1 D.V.M., 19 postdoctoral fellows, 31 M.S., 32 B.S., and 7 A.A.-degreed individuals. Approaches to fulfill the mission bring together research efforts in human risk assessment, genome organization, DNA repair, structural biology, and technology development. A broad-Biotechnology Working Group has been established to overview all biotechnology-related research at Livermore. In addition, the Institute of Genetics and Genomics couples the scientific staff with the academic community to increase student and faculty interaction.

Core competencies in molecular genetics and genomics, DNA repair, human mutation assessment, and molecular toxicology are imbedded in all of the research projects. The Human Genome Center has constructed a high resolution physical map of chromosome 19 and is in the process of identifying the genes on this chromosome and sequencing selected regions. Scientists played a key role with collaborators worldwide in identifying the structural defect in the most common form of adult muscular dystrophy—myotonic dystrophy. In the field of DNA repair, four human DNA repair genes have been isolated and one of them was found responsible for the disease xeroderma pigmentosum type D.

Proteins are being isolated for two of these repair genes to study their structure and biochemical function. In addition, researchers are creating transgenic mice defective for these repair genes. The researchers take pride in the highly interactive team dedicated to the development, validation, and application of methods to assess mutations in humans. Many of the biomarker tools have been developed at Livermore, such as the automated erythrocyte glycophorin mutation assay and chromosome painting. The latter is used to identify chromosomal rearrangements in somatic cells and aneuploidy in sperm. These methods are coupled to traditional methods of somatic and heritable mutation analysis for studies on exposed human populations and for assessments of genetic instability in "unexposed" people. An excellent analytical and synthetic chemistry expertise is the trademark of the molecular toxicology efforts. Using the accelerator mass spectrometer in collaboration with the Geosciences and Environmental Research Program, the researchers quantitate DNA adduct damage at the lowest recorded levels and link the damage to exposure and to its metabolism. Novel instrumentation is developed to support the research, including a high speed flow cytometer and sorter for cell and chromosome analysis/purification, imaging systems for chromosome analysis, robotics for DNA manipulations, and new electrophoresis devices for high throughput DNA sequencing. The researchers have initiated a major thrust in structural biology, including protein crystallography, x-ray diffraction, and computational modeling, which will examine the structure and function of repair proteins and those proteins involved in packaging DNA in sperm. This program is heavily committed to education, collaboration, and technology transfer.

This year, the program is sponsoring more than 50 students and 21 visiting scientists. Most of the students enter through the summer program; others are in residence to attain an advanced degree at one of the collaborating universities. A team research environment is fostered internally, and collaborations are encouraged worldwide. In the Human Genome Center alone, more than 150 active collaborations are maintained. These include interactions with other research institutes, universities, and industry. The researchers have provided materials, know-how, and use of facilities to qualified scientists. Technology transfer has a high priority. Several interactions have been developed with industry, and many endeavors have resulted in licenses. These endeavors include developments in flow cytometry, diagnostic antibodies and DNA primers, chromosome painting probes, and software.

Geosciences and Environmental Research Program

The Geosciences and Environmental Research Program has as its principal mission the understanding of mechanisms and consequences of both synthetic and natural hazards and releases in the geosphere and biosphere. The largest OHER-supported activity within the program is the computer modeling of Earth system processes in the Global Climate Research Division. The Division participates in the Computer Hardware, Advanced Algorithms, and Model Physics (CHAMMP) Program and carries out the Project for Climate Model Diagnosis and Intercomparison. These efforts model the fundamental chemistry and physics processes of the atmosphere, ocean, and biosphere and integrate them into models that can predict the effects of anthropogenic releases to the environment. In consequence of this expertise, the program also operates the Defense Program-supported Airborne Release Advisory Capacity (ARAC), an applied meteorological systems group capable of 24-hour per day prediction of the movement and fallout/rainout of toxic and radioactive materials released by accidents. The Regional Atmospheric Sciences Division, operator of ARAC, also is a participant in OHER's Atmospheric Radiation Measurement activity, providing experimental as well as modeling capability to that component of the climate change research activity.

The Health and Ecological Assessment Division has broad capabilities to assess the impact of releases of toxic and radioactive materials into the biosphere and to trace their movements through it. These capabilities include direct measurement of radiation and toxic concentrations, dosimetry of genetic change in organisms (including humans), and prediction of ecological effects of releases or climate change. The Division operates the Marshall Islands Dosimetry Project, assessing the risks associated with and the procedures necessary for resettlement of these islands. Staff of the Division, in collaboration with the Center for Accelerator Mass Spectrometry, have been carrying out the reassessment of neutron exposures at Hiroshima and Nagasaki and are preparing to perform similar dosimetry for radio-iodine exposures resulting from the reactor fire at Chernobyl. The Center for Accelerator Mass Spectrometry, in association with

collaborators in both the Biology and Biotechnology Research Program and the Nuclear Chemistry Division of LLNL's Test Program, carry out a broad spectrum of isotopic measurements in support of biomedical dosimetry and clinical research and fundamental mechanisms of geochemistry and climate change investigations. The Earth Sciences Division has LLNL's fundamental capabilities in geoscience areas such as subsurface transport and seismic processes, supporting not only environmental research programs but treaty verification, underground nuclear test containment, and seismic hazards assessment and mitigation.

The Geosciences and Environmental Sciences Program has a staff of approximately 150 and a budget of \$30 million, much of it controlled by other LLNL programs to whom scientific and technical support services are provided. The program has extensive collaborations with the external academic community, not only through individual research projects but through the formal mechanisms of the institute for Geophysics and Planetary Physics of UC (which has an LLNL branch) and through the Center for Accelerator Mass Spectrometry and the developing Risk Sciences Center. Collaborations exist with all nine campuses of the University of California, a large number of U.S. and foreign universities and research agencies, and industry. The program provides opportunities for student research and employment and has a large number of postdoctoral fellows performing fundamental and applied research in its disciplines.

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Los Alamos National Laboratory **FY 1992 Budget: \$23.4 Million**

The DOE/OHER-sponsored Health and Environmental Research Program at the Los Alamos National Laboratory consists of research programs in environmental research, health effects, general life sciences, carbon dioxide research, and medical applications.

The Health Effects and General Life Sciences Programs are conducted in the laboratory's Life Sciences Division. The

mission of the Life Sciences Division at Los Alamos is to serve the Nation's needs in health, energy, and national security by addressing a broad range of biological problems at the molecular, cellular, and physiological levels. The major objective of the Life Sciences Division is to understand the health effects of different radiation and chemicals. Research projects in the division address the molecular mechanisms of mutagenesis, DNA repair, and the regulation of gene expression.

The Human Genome Program is part of the nationwide effort to physically map human genes and eventually sequence human genomes. Major research activities are directed to chromosome sorting, to developing human chromosome libraries, and to the physical mapping of chromosomes 16 and 5. Chromosome-specific cosmid, phage, and yeast artificial chromosome libraries have been constructed and characterized. Concise ordering of chromosome 16 loci is nearing completion, using large DNA fragments from specific chromosome libraries. In collaboration with the Chemistry and Laser Sciences Division, a major effort is underway to develop advanced DNA sequencing methods based on single molecule detection. This effort has the potential to revolutionize DNA sequencing methods. Large fragment DNA analysis in the range of 10 to 40 kb has recently been demonstrated using enhanced flow cytometric techniques.

The Structural Biology Research Program focuses on determining the structure/function relationships of biological macromolecules. The DNA sequence database from the Human Genome Project is important for two major problems in structural biology, which are being pursued. The first problem is the DNA organization, structure, and function of chromosomes at all levels down to the nucleosome. The second one involves moving from linear DNA coding sequences to three-dimensional protein structures and their functions. Major projects are concerned with the organization of chromosomes, particularly the functions of repetitive DNA sequences, such as those that led to our identification of the human telomere DNA sequence. The presumptive human centromere sequence has now also been identified. The researchers continue to build on successes in structural biology using in-house capabilities in x-ray scattering and high flux neutron scattering. These techniques are being used to develop a definitive model for the structure of gene 5 protein of fd bacteriophage complexed with single stranded DNA.

The Radiation Biology Program focuses on determining the molecular mechanisms of radiation damage in living organisms and the limits and consequences of low levels of radiation exposure. Projects concerning the mutagenicity of low doses of ionizing radiation address the problems of identifying the primary genetic lesions of radiation damage. A recent success has been the cloning of the human excision repair gene ERCC-5. The complete gene coding sequence of this gene has now been determined as well as its complete exon-intron structure.

The National Flow Cytometry Resource located in the Life Sciences Division provides unique cytometric instrumentation

for biomedical research programs and chromosome sorting for the Human Genome Project. Phase-sensitive detection and Fourier transform flow cytometers are being used to resolve the fluorescence lifetimes of fluorochromes and fluorochromes with overlapping emission spectra. New digital data acquisition systems, incorporating cutting-edge electronics, computer, and programming techniques, are being developed. Very high speed optical sorters and fast kinetic analysis are being developed for chromosome sorting and structural studies of cell surface binding pockets.

The Pulmonary Biology Toxicology Program focuses on the cellular, biochemical, and molecular mechanisms involved in lung defense, acute lung injury, and lung repair. Multiparameter flow cytometric techniques are being applied to selectively harvest specific lung cell subpopulations from the lung's alveolar space and interstitial compartments for subsequent in vitro investigations. Particular emphasis is being placed on understanding the roles subpopulations of pulmonary macrophages play in providing the lung with defense against inhaled particles and on interactions of these subpopulations with other subpopulations of lung fibroblasts in the context of pulmonary fibrogenesis.

The Life Sciences Division is unique in its multidisciplinary approach to problems of cellular and molecular structure and function. Informatics, robotics, laser chemistry, neutron scattering, and cytometry are a few of the examples of its multidisciplinary approach. The Division is heavily committed to collaborations with investigators with similar interests as exemplified by the large number of collaborators hosted by the National Flow Cytometry Resource every year. Several staff members hold joint appointments at the University of New Mexico School of Medicine, where they teach courses and also at the University of California, Davis. Regional high schools are offered a very popular class in molecular and cell biology taught by staff members on a voluntary basis and after hours. In 1992, the Life Sciences Division led the laboratory in patents with 20 percent of the total including the outstanding patent of the year award. The Division is involved in the first Cooperative Research and Development Agreement signed by any of the DOE defense laboratories.

The Atmospheric Radiation Monitoring (ARM) Program, which is conducted in the Earth and Environmental Sciences Division, is a multilaboratory climate research program. The program's goal is to improve the confidence levels of climate prediction by creating better parameterizations of clouds and their effect on the radiative balance of the atmosphere.

Los Alamos participates in the management, field site development, and model development phases of the program. The objectives of the Los Alamos program are consistent with the overall program objectives and stress the combined impact of modeling and observations as the best way to achieve reliable progress in understanding and predicting clouds and energy transfer. Particular tasks address the physics of cloud

formation, variability of the surface-atmosphere interface in the energy exchange, observation of scattering properties of the atmosphere, and the establishment of semipermanent field observatories.

The special capabilities that Los Alamos brings to the program include numerical modeling of atmospheric processes on multiple scales of space and time, the definition and execution of field experiments, and the interpretation of data in terms of innovative analysis methods and the coupling with model calculations. Our role in the management of the program includes the coordination of site operations for the whole suite of five long-term observatories and the setup of the specific facility in the tropical western Pacific region. The latter requires a complex planning effort and a wide range of technical and interpersonal skills.

In addition to the ARM Program, Los Alamos has contributed to interagency research by fabricating, testing, and using ground-based remote sensors. In particular, we fielded a Raman Lidar during the recent shipboard transect of the central Pacific, the Central Equatorial Pacific Experiment (CEPEX), aimed at evaluating the hypothetical thermostat of the Pacific due to the role of cirrus clouds.

The DOE Computer Hardware, Advanced Mathematics, and Model Physics (CHAMMP) Program, which is conducted in the Computing and Communications Division, Theoretical Division, and the Earth and Environmental Sciences Division, as well as the Institute for Geophysics and Planetary Physics, supports the development of global climate models on massively parallel computers, numerical techniques well suited to such computers, improved parameterizations of subgrid-scale physical processes that arise in such models, and research on climate predictability. The CHAMMP Program has two multi-institutional components: a directed effort in "model development" focused on the efficient implementation of atmospheric and oceanic models on massively parallel computers, and proposal-based "science projects" covering the latter three areas.

Los Alamos has a major effort within CHAMMP on development of global ocean models and also has three funded science projects dealing with numerical methods for ocean models and theoretical aspects of ocean predictability. In less than 2 years, this work has produced three papers published in refereed journals, two more that have been accepted, and several that are in preparation. Two three-dimensional ocean models have been redesigned and rewritten for the Connection Machine using the data-parallel Fortran programming paradigm. One is a global Eulerian-coordinate model of the Bryan-Cox-Semtner type; the other is an basin-scale isopycnal model developed by Dr. Rainer Bleck (the University of Miami).

Both models are running in production mode on the Connection Machines (CM-200 and CM-5) in the DOE High Performance Computing Research Center at Los Alamos. This center is one of two established by DOE in support of research on

"grand challenge" problems, and it is partially supported by the CHAMMP Program as a resource for CHAMMP scientists nationwide.

Nine Los Alamos scientists, primarily computational physicists and applied mathematicians, participate in our research and model development activities. This ocean modeling work is being done in collaboration with scientists at the Geophysical Fluid Dynamics Laboratory (NOAA) in Princeton, NJ; the Naval Postgraduate School (DOD) in Monterey, CA; the National Center for Atmospheric Research (NSF) in Boulder, CO; the University of Miami; and the Max Planck Institute for Meteorology in Hamburg, Germany. One Los Alamos scientist also directs the multi-institutional CHAMMP model development effort, which involves four DOE laboratories and the National Center for Atmospheric Research.

Medical applications programs include activities in radioisotope production and imaging function in the human brain. Radioisotope production is carried out at the Los Alamos Meson Physics Facility (LAMPF) by the Isotope and Nuclear Chemistry Division. Collaborations to develop applications of radioisotopes such as ^{67}Cu , ^{89}Sr , and ^{86}Rb have been established with the Cancer Center, the Center for Non-Invasive Diagnosis (CNID), and the Radiopharmacy Department at the University of New Mexico (UNM), Hunter College/CUNY, the Mayo Clinic, St. Mary's Hospital in Grand Junction, Colorado, Johns Hopkins University in Baltimore, Maryland, the National Cancer Institute of the National Institutes of Health, and the University of Texas Health Science Center in Houston, Texas. Efforts with Mayo Clinic are directed at evaluating the ^{67}Cu labeling methodology for possible clinical applications in myasthenia gravis treatment. Work with St. Mary's Hospital, Johns Hopkins University, and the National Cancer Institute is directed at the early detection of lung tumors and possible noninvasive therapy using the ^{67}Cu labeled porphyrin. The collaboration with the University of Texas Health Science Center is focused on obtaining phantom ^{75}As positron emission tomography images to make a preliminary determination of the potential of the $^{75}\text{Se}/^{75}\text{As}$ biomedical generator.

Imaging function in the human brain is conducted by personnel in the Physics Division using magnetoencephalography (MEG). Los Alamos has several small MEG facilities and is in the process of constructing a large sensor array for the brain and a prototype cardiac sensor. The technology development includes superconducting sensors, theoretical models of electromagnetism in the brain, algorithms for functional imaging with magnetic resonance imaging comparisons, and advanced computer software and hardware. Clinical trials of MEG are being conducted as part of the Center for MEG, which is a Los Alamos/Veteran's Administration Medical Center/University of New Mexico collaboration utilizing MEG facilities at the Albuquerque VA Medical Center.

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Oak Ridge National Laboratory
FY 1992 Budget: \$27.9 Million

Oak Ridge National Laboratory (ORNL) is a multiprogram national research and development center with primary missions in energy and environment. It is managed by Martin Marietta Energy Systems, Inc., for the U.S. DOE. OHER-sponsored research is carried out primarily in the Divisions of

Biology, Environmental Sciences, and Health and Safety Research. Several other ORNL Divisions contribute expertise to multidisciplinary projects: Analytical Chemistry; Chemical Technology; Energy; Engineering, Physics, and Mathematics; and Instrumentation and Controls. In addition, two unique user facilities are supported by OHER: the Oak Ridge National Environmental Research Park and the Bioprocessing Research Facility. The latter integrates physical resources from the Biology and Chemical Technology Divisions to include modern flowthrough bioreactors, a flow cytometry laboratory, large volume fermenters, and centrifugal analyzers. Users of these facilities include staff of national laboratories and industry as well as students and faculty from universities. Each of these divisions has unique capabilities and goals; however, strong interactions among the three are a key feature of ORNL's interdisciplinary and collaborative research environment.

The Biology Division investigates potential adverse health effects of energy-related substances. Almost all of the work is experimental and uses mammalian and submammalian systems to obtain data for predicting and understanding human health hazards as well as biological repair. Biology researchers are working on several energy-related substances, such as complex mixtures of chemicals, as well as the effects of neutron and heavy ion radiation. The division is organized into multidisciplinary sections, which investigate the major disease endpoints: mutagenicity, reproductive disorders, carcinogenicity, and acute and chronic toxicity. A necessary part of such studies is the parallel investigation of the normal structure and function of the body and ways the body responds to injury. The studies range in scale from molecular and cellular to the whole animal level. Particular attention is paid to skin and the respiratory tract—two major interfaces between the body and environmental agents.

The Environmental Sciences Division (ESD) was organized in 1972 to consolidate ORNL's pioneering research in radioecology and in waste management, which began in the 1940s. The Division is now one of the largest single-unit environmental research laboratories in the world. Interdisciplinary teams of biologists, geologists, chemists, and physical scientists from ORNL perform problem-oriented research, environmental assessments, and environmental engineering. The division also plays a key role in resolving national environmental problems related to the operation of conventional energy systems. It has achieved international recognition for work on acid deposition, climate, landscape ecology, hazardous waste management, environmental assessment/risk analysis, biogeochemical cycling, development of biomass energy systems, air and water quality research, and environmental database management. The ORNL Center for Global Environmental Studies draws extensively on division staff and resources. ESD's complex research and development mission is accomplished through many cooperative arrangements with universities and private industry. In addition, active programs for visiting scientists, undergraduate, and graduate students are ongoing.

Research in the Health and Safety Research Division is directed toward improved knowledge of the detection and bioeffects of energy-related chemical and physical agents. This rather broad mission encompasses projects that span the range from fundamental physics of atoms and molecules via development of monitoring instrumentation to the study of environmental transport of pollutants, exposure of workers and the public, and potential health impacts. The former studies use state-of-the-art lasers, mass spectrometers, and electron microscopes to probe the underlying chemical and radiation physics important to the division's mission. Application-driven programs include development of advanced pollutant monitoring techniques using, among others, fiber optics or fluoroimmunoassay techniques, and the synthesis of improved radiopharmaceuticals for heart-imaging devices. Ongoing field projects include indoor air pollution measurements and radiological assessment. Experimental and/or computational efforts involving dosimetry, human health risk assessment, and epidemiology are also carried out in the division. The diversity of the background and interests of the division's staff scientists, physics (atomic and molecular, radiation, health physics); chemistry (physical, analytical, organic, biochemistry); biology (biophysics, environmental biology, public health, epidemiology), leads naturally to novel interdisciplinary projects and a stimulating, academic-like environment.

The human genome research has diverse aspects that involve six or more divisions of the laboratory. These fall into two broad categories: one is the investigation of the mouse genome and demonstration of how it gives insight into the human genome. The second is the development of new, faster physical techniques to map and sequence a genome and of innovative computer methods to perform pattern recognition and understand the organizational structure of the genome. The major objective is to explore the structural and functional characteristics of the mammalian genome by use of experimental molecular genetics. Because many parallels exist in the anatomy and physiology between man and mouse, mutations in the mouse are powerful tools for analyzing the structure and function of the human genome.

Joint programs in bioprocessing research and development continue to grow. Expertise in protein chemistry and molecular genetics is combined to continue a research initiative in protein engineering and bioprocessing. This initiative is linked to other important ORNL research activities such as x-ray diffraction methods, determining detailed protein structural information, gene sequencing, protein chemistry, and three-dimensional computer graphics. By using the sophisticated techniques of molecular biology, the laboratory plans to modify genes directly to alter the structure of proteins in a predictable manner, thereby altering functional properties. The techniques for enzyme engineering have opened new vistas for innovative biotechnology. A concerted effort has been initiated to develop a new, advanced family of bioreactor systems that can take advantage of the results of applied biological research as well as modern engineering practices.

OHER-funded divisions at ORNL are heavily involved in a number of key educational activities that support DOE's initiatives in science education. ORNL continues to expand the Ecological and Physical Sciences Study Center, which is one of the most visible and successful precollege programs. ORNL also hosts the annual DOE National High School Science Honors programs, which in recent years have addressed environmental issues. The Special Honors Study Program allows exceptional high school students to conduct a study project at ORNL under the supervision of a staff member. The Biology Division is home to the University of Tennessee-Oak Ridge Graduate School of Biomedical Sciences, which for the past 25 years has trained some of the Nation's leading biologists. Now in its second decade, the University of Tennessee Graduate Program in Ecology is a collaborative effort with ESD.

OHER-funded researchers at ORNL are heavily involved in technology development and transfer activities. In the past 5 years, researchers in the ORNL BER Program have filed more than 25 patents and have completed 5 license agreements for a wide range of technologies. To date, seven BER-related cooperative research and development agreements have been initiated. Research and development activities affiliated with ORNL's BER Program have received a number of national technology-based awards, including 19 R&D 100 Awards.

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Pacific Northwest Laboratory

FY 1992 Budget: \$32.9 Million

Operated by Battelle Memorial Institute, the Pacific Northwest Laboratory (PNL) is headquartered at the Hanford site in Richland, Washington. Current PNL programs sponsored by DOE's OHER include: (1) health effects research, focused on molecular and cellular mechanisms of damage by chemicals and radiation; (2) research on biological and environmental interactions of radon and other alpha-emitting radionuclides; (3) radiological and chemical physics of biological damage mechanisms; (4) environmental research (subsurface science and terrestrial ecology); (5) atmospheric physics and chemistry; and (6) climate research.

In the PNL research conducted for OHER, an increased emphasis is being placed on gaining a detailed molecular-level understanding of the interactions of chemicals and radiation with biosystems and the ways in which these interactions are manifested in the environment. Studies of this nature are the focus of two major new PNL programs—the Environmental Science Research Center (ESRC) and the Molecular Science Research Center. Molecular sciences research supporting these programs will be housed in the Environmental and Molecular Sciences Laboratory (EMSL), a 200,000 ft² laboratory scheduled for completion in 1996. EMSL will be a national collaborative research center containing equipment specifically developed to address molecular-level problems in complex environmental systems. In another major new activity, PNL is providing support to DOE in the Atmospheric Radiation Measurement (ARM) Program, a U.S. global environmental change research program.

Atmospheric Sciences and Climate Change Research

The PNL atmospheric sciences and climate change research programs are focused on understanding the local-to-global scale effects of energy-related pollutants on air quality and climate. This research is conducted to support various DOE missions, including the development of energy supplies that are both environmentally benign and capable of meeting the energy needs of a growing, internationally competitive economy.

PNL has a lead role in five major atmospheric sciences and climate change research programs within the OHER Environmental Sciences Division. In the Atmospheric Chemistry Program (ACP), the fate of energy-related pollutants is examined through research on cloud and precipitation chemistry, cloud microphysics and dynamics, and global-scale transport. The Atmospheric Studies in Complex Terrain (ASCOT) Program applies research on the dynamics of air flow in hilly to mountainous terrain to problems of pollutant dispersion in complex terrain, an issue of importance in emergency preparedness at DOE facilities and other sites. The ARM Program is designed to improve basic understanding of the effects of clouds on radiative transport through the Earth's atmosphere and to develop better representation of clouds and their radiative

effects in climate models. Research within the Oceans Research Program focuses on processes governing the exchange of greenhouse gases between the ocean and atmosphere and on physical processes that cycle heat and carbon between the surface and deep ocean. The Computer Hardware, Advanced Mathematics, and Model Physics (CHAMMP) Program conducts research designed to improve climate modeling by coupling advances in computer hardware, specifically parallel computing architectures; improved computational techniques and better representations of essential physical processes should achieve an increase in the computational throughput of these models by a factor of 10,000. Finally, PNL contributes to DOE research on the global carbon cycle through its continuing development of models for predicting emission of carbon dioxide and other greenhouse gases both from energy production and utilization and from other human activities.

Research programs at PNL in the areas of atmospheric sciences and climate change support the development and implementation of a National Energy Strategy by DOE. Integrated multilaboratory field studies, theoretical analysis, and numerical modeling studies are advancing the understanding of atmospheric processes and enhancing the ability to simulate critical climate processes in computational models. Other research areas of continued emphasis include investigations on the continental and oceanic fate of energy-related air pollutants at the molecular level, where critical interactions and exchange processes at interfaces between environmental media are least well understood. Cloud process research is being extended to studies on the transport, transformation, and removal of pollutants on the global scale; the effects of pollutants on the radiative properties of clouds; and the role of cloud processes in producing radiatively active aerosols.

Environmental Sciences

Environmental research is focused on understanding the mechanisms by which key physical, chemical, and biological processes function together in terrestrial and subsurface systems to control the transport, transformation, and effects of chemicals and other stressors in the environment. In conjunction with laboratory studies, unique intermediate-scale and field facilities in subsurface and terrestrial environments are being used to analyze basic processes and to validate predictive models. Advanced sampling techniques and scaling concepts and models are under development for extrapolating mechanistic knowledge to larger systems for application in environmental restoration and mitigation of stressor effects.

The PNL Environmental Research Program has played a key role in OHER's broader program in Subsurface Science and Terrestrial Ecology. The Subsurface Science Program brings the disciplines of geology, hydrology, microbiology, molecular biology, and geochemistry to bear in studies of mixed contaminant behavior in the subsurface, the understanding of which is critical for predicting impacts on groundwater. The PNL ESRC is conducting fundamental research on subsurface processes of

importance for environmental restoration, including deep subsurface microbiology and subsurface heterogeneity. Particular emphasis is being placed on defining the origins and functions of microbial communities in the deep subsurface environment and on basic research related to the use of natural systems in remediating deep subsurface contamination in situ. University outreach efforts have involved more than 35 universities in the Subsurface Science Program and technology transfer activities.

The Terrestrial Ecology Program focuses on understanding the fundamental processes that control water and elemental fluxes across soil, plant, and atmospheric boundaries. Advanced modeling and satellite observations are being used to extrapolate this knowledge to the landscape level for assessing the effect of global change and for managing the recovery of stressed arid land systems. A new initiative is directed toward using molecular tools to examine specific mechanisms controlling various ecosystem adjustments to environmental change.

Health Effects Research

Health effects research is addressed through a multilevel program incorporating studies from the molecular to whole-animal levels. Emphasis is placed on gaining a quantitative understanding of the mechanisms that underlie the effects of radiation and chemicals using integrated dosimetric, molecular, cellular, and animal studies. The Health Effects Research Program focuses on basic studies to test hypotheses concerning the interaction of chemical and physical agents with molecules in biological systems and the alteration of these molecules by the transfer of energy. Perturbations in macromolecular structure and genetic processes are being investigated both in vivo and in vitro as indicators of disease susceptibility and causation by radiation and toxic chemicals.

This program strongly emphasizes research on the biological interactions and health effects of high linear-energy-transfer (LET) radiation, including studies on transuranic elements and radon. This research includes investigations on the interactions of high LET radiation with critical biological targets such as DNA and the expression of genetic damage in exposed cells and in vivo animal tissues. A new microbeam technique for single-cell irradiation using alpha particles will contribute to the understanding of mechanisms of action and biological effectiveness of high LET radiation.

A major new initiative in this research area involves the study of perturbed molecular structures and their relationship to altered functional properties of DNA, RNA, and proteins in cells and tissues exposed to radiation or toxic chemicals. A wide variety of advanced spectroscopic techniques, such as high field nuclear magnetic resonance (NMR) at frequencies of 500 to 1,000 MHz, is becoming available at PNL for characterizing the solution structures of large biological macromolecules. This instrumentation will be used in studies of changes in DNA conformation and DNA-protein interactions that result from damage by ionizing radiation and toxic chemicals.

Structural Biology and Genome Research

The new EMSL facility will contain advanced spectroscopic and computational techniques for research in chemistry, materials science, biochemistry, and environmental science. The massively parallel computing systems and leading-edge spectroscopy techniques such as NMR at frequencies as high as 1,000 MHz, pulsed electron paramagnetic resonance spectroscopy, a 12-tesla ion cyclotron resonance mass spectrometer, and numerous optical spectroscopies will provide exceptional capabilities for experimental and theoretical studies on the structure and dynamics of biological macromolecules and environmental systems.

Research related to the Human Genome Project and molecular dynamics simulations on large macromolecules such as P450 enzymes have been initiated using existing supercomputer and spectroscopic instrumentation that will ultimately be surpassed in the EMSL facility. New OHER projects at PNL that utilize advanced spectroscopic and computational facilities include the use of a 7-tesla ICR-MS system for rapid DNA sequencing and a theoretical program on rational enzyme redesign for bioremediation applications.

Analytical Technology

Measurement science and dosimetry research programs are developing more accurate and sensitive techniques for measuring physical and chemical processes in environmental and biological systems. Laser spectroscopy techniques are being developed for trace-level detection of chemical agents and are being applied in the study of biologically important molecules such as nitric oxide and their interactions with larger molecular structures. Sensitive mass spectrometry techniques are being applied to the detection of extremely low levels of DNA adducts formed by pollutant interaction. Other analytical research is focused on characterizing the physicochemical mechanisms of trace contaminant transport, deposition, and fate in the environment and in biological systems.

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SPECIAL PURPOSE LABORATORIES

Ames Laboratory Iowa State University FY 1992 Budget: \$644,000

The thrust of the Ames Laboratory's Health and Environmental Research program is directed toward the conception, development, and use of advanced measurement techniques that will alleviate analytical inadequacies by improving both reliability and sensitivity. Efforts are focused on identifying and correcting problems in existing methods and techniques and devising less complicated and more reliable approaches. These efforts cover a broad scope including basic studies, the design and assembly of new types of instrumentation, and the evaluation of new and existing analytical procedures for all types of environmental and biomedical analysis. Specific goals of this effort are (1) to devise experimental approaches that provide unique information in studies of DNA damage and chemical carcinogenesis and (2) to develop new methodology for gene mapping and for DNA sequencing.

Facilities and Personnel

The Ames Laboratory has one of the world's strongest and most consolidated analytical measurement efforts. Included on the staff of the Health and Environmental Research Program are four senior scientists, all of whom have established international reputations and are the recipients of at least 21 national or international awards. Ames Laboratory possesses extensive analytical facilities for determining trace levels of toxic organic and inorganic constituents in a variety of environmental and biological samples, including state-of-the-art laser-based instrumentation based on concepts developed at the laboratory. Therefore, the laboratory is in an excellent position to conduct basic research on new analytical measurement concepts and to demonstrate their utility in the field of chemical carcinogenesis

and gene mapping and DNA sequencing. The current OHER funding level is 7.20 direct and 3.60 indirect FTE. The Ames Laboratory is also unique in that the majority of the scientific staff is graduate students and postdoctoral scientists. Training of future scientists is a major component of the OHER-funded effort. Currently, six graduate students and one postdoctoral scientist are working on the above OHER projects. Three Ph.D. theses based on these projects have been approved in the past year.

Scope, Focus, and Emphasis

Advanced analytical concepts are conceived and developed, and existing techniques are refined so that reliable measurements can be made on the concentration of toxic inorganic and organic pollutants that occur as trace constituents in environmental and biological samples. These innovative instrumental techniques are being used for biomedical applications such as the characterization and quantitation of organic carcinogen-DNA adducts and for the measurement of actual dosages experienced by receptors following exposure to carcinogens. These researchers have successfully detected DNA adducts associated with the carcinogen benzo[a]pyrene and differentiated between adducts formed by different metabolic routes. These new techniques are being applied to in vivo and in vitro studies of DNA damage and chemical carcinogenesis. The researchers are also developing novel approaches to detection and separation in electrophoresis. Results indicate that substantial savings in time and effort in gene mapping and DNA sequencing applications should be possible. Specific emphasis includes the development of sensitive real-time monitoring techniques to allow interactive control during electrophoresis and optical and separation schemes that allow simultaneous highly multiplexed fluorescence detection to speed up DNA sequencing.

Collaborations

Laser-Based Studies of DNA Damage and Chemical Carcinogenesis

Advanced research on chemical carcinogenesis of the type described previously requires extensive and active collaboration between physical and biochemical/toxicological scientists. To this end, collaborations have been established with several well-known carcinogenesis groups: N.E. Geacintov (Chemistry Department, New York University); U. Varanasi (National Oceanic and Atmospheric Administration, Seattle, WA); E. Cavalleri and E. Rogan (Epopley Institute of Cancer Research, Omaha, NE); and D.M. Phillips (Institute of Cancer Research: Royal Cancer Hospital, London, England).

Quantitation in Electrophoresis Based on Lasers

Newly developed separation and detection methods must be evaluated during actual mapping and sequencing runs. For this, collaborations have been established with the group headed by B. Karger (Chemistry Department, Northeastern University, and a DOE Human Genome grantee), who will provide the

researchers with state-of-the-art capillary gel column technology. Expertise in lasers and optics should also benefit the OHER-funded effort by providing sensitive detection for their studies.

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Environmental Measurements Laboratory

FY 1992 Budget: \$7.1 Million

Role and Objectives

The Environmental Measurements Laboratory (EML) is a Government-owned, Government-operated laboratory, programatically under OHER. The laboratory is administered by the Chicago Operations Office (CH). The laboratory has been in existence for 45 years, having descended from a small group involved in industrial hygiene-type activities associated with the Manhattan Project at the end of World War II.

EML's mission is to conduct experimental and theoretical research concerning radioactive and other energy-related pollutants in the environment to address important scientific questions related to human health and to environmental impact. Through its multidisciplinary staff, EML provides DOE and other Federal agencies with the in-house capability needed to respond effectively and efficiently to current environmental and related national security issues.

EML is an internationally recognized unique environmental research facility, integrating the physical, chemical, and biological sciences. This facility conducts multidisciplinary investigations at local to global scales of current or anticipated concerns to DOE and the Federal Government and functions as the comprehensive and authoritative Quality Assurance Laboratory for DOE in environmental measurements, sampling, and analysis.

EML participates in activities in the scientific community both nationally and internationally. Instrumentation and methodology developed at EML have been transferred and marketed commercially for a number of years. The Procedures Manual, HASL-300, has achieved major recognition in both the national and international community as a definitive document of radioanalytical methods and techniques. EML engages in a significant amount of collaborative research with other institutions throughout the world, including government agencies, national laboratories, and universities. Other activities include hosting international visiting scientists, scientific lectures to

students at all levels of education, presentations at career-related workshops, participation in training programs of the International Atomic Energy Agency, and facility tours for students and visitors to the laboratory. Other cooperative programs have included employment of college summer interns and volunteer work/study assignments by high school science students.

Staff and Facilities

Included among the staff of 91 employees are 56 scientific researchers and 16 technicians who are engaged in various diverse research disciplines. They participate actively in professional society activities, serving as officers of national organizations or local chapters and as members on national and international committees, standards institutes, and task forces. Many are affiliated with educational institutions as adjunct professors, guest lecturers, and curricula advisors.

The laboratory is located at the southern end of Manhattan in New York City, occupying approximately 75,000 square feet of laboratory and office space on the fifth floor of a 12-story government building.

Specialized facilities include:

- The *Clean Room Laboratory* with class 100 air for ultralow-level analytical measurements.
- The *Scanning Electron Microscope* for detailed chemical and morphological classification of aerosol particulates.
- The *Radon Calibration Chamber*, one of only four internationally recognized radon reference facilities worldwide, for radon/radon progeny experiments.
- Since 1958, EML has supported a worldwide network of *Global Fallout and Surface Air Sampling Stations* to study the global distribution of radioactivity released into the atmosphere from nuclear bomb testing, to measure debris from events such as reactor accidents, and to analyze samples for natural radionuclides. The Remote Atmospheric Measurements Program, an extension of the Global Fallout and Surface Air Sampling Program, provides wider coverage and a more rapid measurement response capability (within 48 hours) via satellite from very distant stations around the world.
- The van-based *Mobile Laboratory* for environmental radiation measurements and sample collections at remote continental locations.
- The *Lake-Sediment Coring Boat* for sediment core collection in lakes throughout the United States.
- The *Rural Field Site* at Chester, New Jersey, for regional baseline monitoring and field testing of instrumentation.
- EML's *Sample Archives* of more than 65,000 samples of environmental and biological matrices dating back more

than 40 years for retrospective or quality assurance investigations.

Research in Progress

EML's research is integrated into the following six program areas:

- Environmental Radiation and Radioactivity
- Radiation Transport and Dosimetry
- Environmental Radon, Thoron, and Related Aerosols
- Atmospheric and Surface Pollutant Studies Related to Global Climate Change
- Ecological and Subsurface Pollutant Research
- Metrology, Consultation, and Emergency Response

In carrying out its mission and pursuing these research areas, EML plans, directs, and executes:

- Research on nuclear and non-nuclear pollutants in both the outdoor and indoor environments.
- Studies of the distribution, composition, mechanism, and rate of movement of nuclear and non-nuclear pollutants from the atmosphere to water, soil, plants, animals, and humans.
- Advanced studies in the development and application of analytical chemistry and radioanalytical procedures for use in determining radioactivity and non-nuclear pollutants in environmental and human samples.
- Research and development of improved instruments for use in detecting and measuring environmental radioactivity and non-nuclear pollutants.
- Radiological and chemical measurement programs to develop data used by the laboratory, other DOE components, other Federal agencies, and international organizations (such as UNSCEAR and the International Atomic Energy Agency) in assessing environmental and human health effects.
- A variety of quality assurance programs ranging from "in-house" to intra- and inter-agency cooperative programs to international intercomparisons.
- Development and critical application of improved methods for measurement and analytical calculation of the properties of natural and anthropogenic radiation sources and fields, and the consequent dose to humans in the environment and the workplace.
- Toxicological investigations of the pathological impact at the cellular level in indigenous organisms of energy-related pollutants in the environment.

- Subsurface hydrogeologic studies of long-lived natural and anthropogenic radionuclides to identify sources of these radionuclides and to quantify their transport and diffusion.

As a Government-owned and operated facility, EML is able to respond rapidly and authoritatively to environmental incidents and issues involving the national interest.

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Inhalation Toxicology Research Institute

FY 1992 Budget: \$7.5 Million

Role and Objectives

The Inhalation Toxicology Research Institute (ITRI) is a Government-owned, contractor-operated Federally funded research and development center. It is managed and operated by the Lovelace Biomedical and Environmental Research Institute, Inc., (LBERI) under a tripartite, cost-reimbursable, no-fee contract between the U.S. DOE, LBERI, and the Lovelace Medical Foundation (the parent organization of LBERI).

As a special purpose laboratory of OHER, the primary mission of ITRI is to support OHER by conducting research addressing information needs related to health risks from inhaled, energy-related materials. As a Federally funded research and development center and a unique national research resource, the broader mission of ITRI is to improve the scientific basis for understanding the biology of the respiratory tract, the pathogenesis of respiratory tract disease, and the impact of inhaled materials on human health. ITRI conducts basic and applied studies using macromolecules, cells, and tissues of human and animal origin, and laboratory animals, to produce information complementing findings from human epidemiological and clinical studies. The materials of concern include those toxic by virtue of their radiological, chemical, or physical nature.

Originating from the need to obtain data on health risks from inhaled radionuclides, ITRI has evolved to become a major national resource for basic and applied research on respiratory biology, respiratory disease, and respiratory toxicology. The Institute is unique in filling an important niche that is complementary to private and academic capabilities. It excels at maintaining the range of personnel and facilities and the team-oriented approach often required to tackle research issues that neither private nor academic institutions are well suited to

address. ITRI is an important resource for industry and is active as a source of information, in transferring technology to industry, in meeting research needs that cannot be met by private or university laboratories, and as a partner in cooperative research and development (CRADAs) ventures. ITRI is an important training resource and has been heavily involved in educational activities for many years. ITRI operates a doctoral program in inhalation toxicology and a National Institutes of Health-funded postgraduate training program in environmental toxicology and epidemiology jointly with the University of New Mexico.

Staff and Facilities

The approximately 170 full-time employees of ITRI include a research staff of about 30 principal investigators and 60 technicians who encompass a broad range of disciplines and experience, including aerosol science, chemistry, toxicology, cellular and molecular biology, radiobiology, pathology, veterinary medicine, biomathematics, and risk assessment. The research is supported by an animal care staff of 20 and the full range of administrative support staff. The hallmarks of the staff are its diversity, qualifications, motivation and productivity, orientation toward excellence, readiness to communicate and collaborate, and a culture of teamwork that crosses institutional and disciplinary lines. ITRI scientists hold more than 50 positions on national and international advisory boards, review panels, and study sections, 15 positions as scientific editors or on editorial boards of scientific journals, and numerous offices in leading professional scientific societies.

ITRI is located on Kirtland Air Force Base East in Albuquerque, New Mexico. It occupies facilities of 289,917 square feet used for offices, laboratories, animal housing, and research support activities. These facilities have an estimated replacement value of \$62 million and contain capital equipment valued at approximately \$15 million. Specialized facilities include (1) inhalation exposure laboratories with the capability for exposure of laboratory animals to gases, vapors, or particles; (2) specialized aerosol research laboratories; (3) analytical chemistry laboratories; (4) molecular biology, toxicology, biochemistry, microbiology, and tissue culture laboratories; (5) facilities for the care and housing of laboratory animals; (6) extensive pathology facilities; and (7) an extensive research library.

Scope of Ongoing Research

ITRI is conducting research which falls into five major programmatic areas:

(1) Characterization of Airborne Materials and Generation of Experimental Atmospheres

The purpose of the research conducted within this area is to develop information on which improved health risk estimates for humans can be based, by investigating basic aerosol characteristics and phenomena that influence the biological fate and effects of inhaled particles and vapors. Areas of study include (1) investigations of the mechanisms of aerosol formation and characterization of the resulting airborne materials, (2) investi-

gations to determine how physical and chemical characteristics of airborne materials influence the biological fate and health effects resulting from inhalation of those materials, and (3) studies to extend the knowledge of basic aerosol properties and behavior.

(2) Metabolism and Dosimetry of Inhaled Toxicants

The underlying theme in this research area is to determine the toxicant doses received by critical units in the respiratory tract (macromolecules, cells, and tissues) and to study the relative influences of various physical and chemical characteristics of the inhaled material and anatomic and physiologic characteristics of the exposed subject. Because of common underlying principles, studies of both inhaled radioactive and chemical toxicants are included in this category.

(3) Carcinogenic Responses to Internally Deposited Radionuclides

In this area, studies are determining the lifespan health risks of both alpha- and beta-emitting radionuclides and a number of important factors that can influence these health risks, such as total dose, dose rate and its temporal patterns, homogeneity of pulmonary alpha dose, age at exposure, linear energy transfer, dose protraction, and interspecies relationships. The information being obtained, analyzed, and published is strengthening the researchers' knowledge of the behavior and effects of inhaled radionuclides and the resulting guides and standards for their safe use. Major emphasis continues to be directed to the review, analysis, modeling, and presentation of the results for the studies in which all dogs are now dead.

(4) Mechanisms of Respiratory Carcinogenesis

The aim of this research area is to improve our understanding of the risk of developing lung cancer from inhaled materials by establishing extrapolation bridges between laboratory animals and people and by delineating the pathogenesis of radiation and chemically induced lung cancer. Genes whose expressions are significantly altered in radiation-caused hyperplastic type II pneumocytes and are thereby putatively involved in the early steps of type II cell carcinogenesis are being identified. Subsequently, the genes will be used as probes to ascertain their temporal patterns of expression in cells or lesions representing different stages of lung carcinogenesis. Finally, the genes will be engineered into an expression vector and introduced into normal, pre-tumorigenic, and tumorigenic type II cells to determine their effect on cell phenotype. Gene dysfunctions are being sought in lung tumors and cells from uranium miners. The frequency of p53 alterations is being determined in premalignant and tumor cells in rats that have inhaled $^{239}\text{PuO}_2$. Gene alterations are also being identified in lung tumors of Beagle dogs caused by inhalation of $^{239}\text{PuO}_2$. In parallel, dysplastic lung tissues are being collected from a new serial-sacrifice cohort of dogs to determine which changes regularly arise during the initial stages of high LET radiation-generated tumors. Another objective is to isolate and character-

ize functional analogues of mammalian cell-cycle regulatory genes such as p53 from yeast. This information will define the links between the p53 tumor suppressor gene and the regulation of the cell cycle and determine how these links are altered in radiation-induced DNA damage. Genetic and epigenetic alterations involved in the development and progression of chemical-induced pulmonary neoplasia are also being identified. Tumor development is being studied following exposure of rodent models to single chemical carcinogens or mixtures. Gene dysfunctions are being examined prior to preneoplasia, during preneoplasia, and in benign and malignant neoplasms.

(5) Noncarcinogenic Responses to Inhaled Toxicants

One objective of this area of research is to determine the biochemical events that are critical in the development of late-occurring pulmonary disease resulting from inhalation of toxic materials. A second objective of this research is to elucidate the mechanisms involved in injury of epithelial cells in upper- and lower-respiratory airways after exposure to inhaled toxic materials. Current emphasis is on determining the mechanisms of toxicant-induced inflammation and mucus hypersecretion and their roles in the pathogenesis of airway response to injury. These responses are important features of many human diseases, such as acute and chronic rhinitis, bronchitis, and bronchopneumonia. A third objective of this research is to identify the mechanisms necessary for the induction of pulmonary immune responses and determine how the inhalation of pollutants may alter immunity in the lung and airways to produce disease. Inhaled pollutants may suppress pulmonary defenses, resulting in increased pulmonary infection and/or lung tumors, and studies will continue to evaluate this possibility. In addition, epidemiology data show that inhaled pollutants may also cause lung disease by stimulation of immunity and increase the incidence of hypersensitivity lung disease including asthma.

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Laboratory of Radiobiology and Environmental Health, University of California, San Francisco **FY 1992 Budget: \$3.0 Million**

Located on the campus of the University of California, San Francisco (UCSF), the Laboratory of Radiobiology and Environmental Health is a basic research institute in cell biology. The laboratory is dedicated to gaining essential molecular biological information that can be used not only for its own sake but also for gaining meaningful insights into how radiation and other energy-related biomedical insults affect normal cellular processes and lead to detrimental genetic and somatic biomedical effects. The purpose of these studies is to gain a fundamental understanding of the mechanisms by which perturbation and repair of cellular systems can affect the whole organism, lead to damage that affects future generations, or even lead to cancer in the present generation, and especially to understand how the organism can cope with such insults. The thrust is not just to catalog the effects, but to gain a basic understanding of how perturbations of normal cellular and physiological processes are initially induced, repaired, and expressed at the molecular, cellular, tissue, and organismal levels of biological organization. At present, the laboratory has five separate but related groups studying cell biology starting from the point of view of DNA replication and progressing through DNA repair, chromosomal effects and cytogenetics, cellular structure, and physiology of the macrophage system to developmental biology.

The laboratory, which is housed in a DOE-owned building, is an organized research unit in the School of Medicine at UCSF. It had its genesis in 1951 as the Radiological Laboratory of the Department of Radiology. This laboratory was established by AEC as a Government-owned, contractor-operated facility to study the effectiveness of radiation from a 70-MeV synchrotron in the treatment of cancer. In 1964, that project was terminated, and the laboratory became a basic cell biology institute. At present, it is a dedicated single-purpose, in-house laboratory of the U.S. DOE with a permanent staff of about 48 people. Visiting scholars and postdoctoral fellows bring the total census of people working within the laboratory to about 90. The laboratory, which is dedicated to basic studies of the processes involved in how radiation and other energy-related health hazards affect normal cellular processes and cause human disease, is an interdepartmental and interdisciplinary unit for research and training in cell biology within UCSF. The principal investigators and the permanent staff at the doctoral level all have appointments in the Department of Radiology at UCSF and cross appointments in various basic science departments.

The faculty is heavily involved in the academic programs of the University. All those faculty with professorial appointments teach their specialties on the campus and participate in various medical school or campus-wide committees important to the governance of the University. A further academic contribution is made through the teaching of large numbers of

postdoctoral fellows from the United States and abroad who seek professional training with the staff of the laboratory.

The laboratory is located in its own building with 11,446 assignable square feet of space, of which 5,700 square feet are for laboratories, 2,300 square feet for offices, and the remaining area for storage, animal rooms, a library, and supporting facilities such as cold room, dark room, instrument rooms, etc. It also has a Philips Model 250 therapeutic x-ray machine that is the only such machine on the campus of UCSF that can be used for research purposes. The building itself is owned by the U.S. DOE, but is on land leased from UCSF.

The research carried out in the Laboratory of Radiobiology and Environmental Health constitutes a comprehensive interdisciplinary attack on basic cell biological problems. The work begins with studies on the fundamental biological molecule, DNA, on how it replicates, is repaired, is organized into genes and chromosomes, and how these essential units themselves replicate, recombine, mutate, undergo repair, respond to injury, and, in general, carry out their function. The research then studies how the genes and chromosomes work in organized cell systems, such as the macrophage system, which has now been recognized as an exceedingly important cell system involved in many complex physiological functions such as tissue breakdown and resynthesis (remodeling), wound healing, inflammation, and metastasis of tumors. Other studies deal with how genes and chromosomes operate during mammalian development and differentiation, i.e., throughout embryogenesis. Within the laboratory, the research groups utilize the new powerful methods of molecular biology that keep the research at the cutting edge of progress. The experiments are essential to any comprehensive understanding of how an organism can respond to insults and perturbations brought about by exposure to radiation or chemical toxicants released during the production of energy and that are teratogenic, mutagenic, and/or carcinogenic.

At any given time, many postdoctoral fellows and numerous people from around the country and the world are in residence at the laboratory. Furthermore, these people, and others throughout the world, are involved in collaborative experiments with the staff. In the past year, the scientists at the laboratory carried out numerous collaborative efforts with scientists from several other departments at UCSF. These include collaborative research with people from the departments of Anatomy, Biochemistry and Biophysics, Dermatology, Epidemiology and Biostatistics, Growth and Development, Laboratory Medicine, Neurosurgery, Pathology, Pharmaceutical Chemistry, Physiology, Radiation Oncology, Radiology, Stomatology, and Surgery, as well as those at the San Francisco VA Medical Center. In addition, numerous extensive collaborative efforts were carried out with people from other institutions here and abroad.

Until recently, the laboratory has been almost entirely supported by DOE. Owing to DOE budgetary constraints and the necessity to meet cost-of-living increases and inflationary pressure, the laboratory became involved in work for others in FY 1987-1988. Currently, it has some National Institutes of Health Work for Others projects that complement ongoing DOE research programs. These projects represent less than 7 percent of the laboratory's total budget. In addition, the laboratory investigators, by virtue of their status as faculty members with cross appointments in various departments, take part in numerous training grants, research projects, and program projects.

Program Contact

Sheldon Wolff

Director

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Abbreviations and Acronyms

Acronym	Expanded Name	Acronym	Expanded Name
2DE	two-dimensional gel electrophoresis	ARS	autonomously replicating sequences
4DDA	four-dimensional data assimilation	a-Sa:H	hydrogenated amorphous silicon
ABL	atmospheric boundary layer	ASCOT	Atmospheric Studies in Complex Terrain
AC	adenine-cytosine	ASI	air-sea interaction
ACM	Advanced Climate Model	AT	ataxia telangiectasia
ACP	Atmospheric Chemistry Program	ATP	adenosine triphosphate
AD	advantage depths	ATPase	adenosine triphosphatase (an enzyme)
ADD	assessment of dominant damage	AVHRR	Advanced Very High Resolution Radiometer
ADICT	Atmospheric Diffusion In Complex Terrain	AVM	arteriovenous malformation
ADPIC	Advection-Diffusion Particle in Cell	BaP	benzo(a)pyrene
ABC	Atomic Energy Commission	BASC	Board on Atmospheric Sciences and Climate
AER	atmospheric and environmental research	BATS	biosphere-atmosphere transfer scheme
AERI/AERI-X	Atmospheric Emitted Radiance Interferometer	BAZ	biologically active zone
AEROCE	Atmosphere/Ocean Chemistry Experiment	BCF	accepted name of a specific strain
ABS	Auger Electron Spectroscopy	BER	biomedical and environmental research
AFM	atomic force microscopy	BioSCAN	biological sequence comparative analysis node
AIM	approximate inertial manifolds	BISP	biological information signal processor
ALARA	as low as reasonably attainable	BLIP	Brookhaven Linac Isotope Producer
ALFA	AER Local Forecast Adaptation	BMRR	Brookhaven Medical Research Reactor
ALK	alkalinity	BNCT	boron neutron capture therapy
ALLOC	generic model of whole-plant response	BNL	Brookhaven National Laboratory
ALS	Arctic Landscape Simulator	BOPP	boronated porphyrin
AMA	American Medical Association	bp	base pair
AMPPD	disodium 3-(4-methoxyspiro [1,2-dioxetane -3,2'-tricyclo[3.3.1.1 ^{2,7}] decan-1-4-yl) phenyl phosphate	BPA	p-boronophenylalanine
AMS	accelerator mass spectrometry	BPDE	BaP-diolepoxide
ANL	Argonne National Laboratory	BSCS	Biological Sciences Curriculum Study
AP	alkaline phosphatase	CaBS	California Basins Study
APM	acoustic plate mode	CAC	Committee on Atmospheric Chemistry
APS	Advanced Photon Source	CAM	crassulacean acid metabolism
ARAC	Atmospheric Release Advisory Center	CAMAC	computer automated measurement and control
ARM	Atmospheric Radiation Measurement	CARDS	climatological aerological reference data set

Acronym	Expanded Name	Acronym	Expanded Name
CART	Cloud and Radiation Testbed	cw	continuous wave
CAT	computerized axial tomography	DARCS	diode-laser absorption remote concentration sensor
CBD	chronic beryllium disease	DAS	data assimilation system
CCD	charge-coupled device	DBMS	database management system
CCM ₁	Community Climate Model One	DEAE	diethylaminoethyl
CCM ₂	Community Climate Model Two	DHFR	dehydrofolate reductase
CCN	cloud condensation nuclei	DIC	dissolved inorganic carbon
CD	circular dichroism	DIDAC	digital data acquisition system
CDIAC	Carbon Dioxide Information Analysis Center	DMBA	Dimethylbenzoic Acid
CDRP	Carbon Dioxide Research Program	DMS	dimethyl sulfide
CDTA	cyclohexanediaminetetracetic acid	DOSAR	Dosimetry Applications Research
CE	capillary electrophoreses	DPA	dual-photon absorptiometry
CBA	cancer embryonic antigen	DSA	differential sensitivity analysis
CBC	Commission of the European Communities	DSM	Deep Subsurface Microbiology
CBES	Committee on Earth and Environmental Sciences	DTPA	diethylenetriaminopenta-acetic acid
CE-MS	capillary electrophoresis with mass spectrometry	DVI	dust veil index
CEPEX	Central Equatorial Pacific Experiment	EBV	Epstein-Barr virus
CGCR	Committee on Global Change Research	ECM	extracellular matrix
CH	Chicago Operations Office	ECMWF	European Center for Medium Range Weather Forecasts
CHAMMP	Computer Hardware, Advanced Mathematics, and Model Physics	EDTA	ethylene diaminetetraacetic acid
CHO	Chinese hamster ovary	EELS	electron energy loss spectroscopy
CIRRPC	Committee on Interagency Radiation Research and Policy Coordination	EBR	Extended Entity-Relationship
CIS	Chromosome Information System	EGF	epidermal growth factor
CM2	connection machine	ELISA	enzyme-linked immunosorbent assay
CNID	Center for Non-Invasive Diagnosis	EML	Environmental Measurements Laboratory
CNS	central nervous system	EMSL	Environmental and Molecular Sciences Laboratory
COHMAP	Cooperative Holocene Mapping Project	EMT	electron microscope tomography
COM	colloidal organic matter	ENSO	El Niño Southern Oscillation
COMFS	Continental Ocean Margin Flux Study	ENU	ethyl nitrosourea
CPMS	Climatological Prediction by Model Statistics	EOF	empirical orthogonal function
CRADA	Cooperative Research and Development Agreement	EPER	Environmental Processes and Effects Research
CRC	Climate Research Committee	EPI	Environmental Productivity Index
CRU	computer resource units	BR	excision repair (gene)
CSU	Colorado State University	ERBE	Earth Radiation Budget Experiment
CT	computed tomography	ERDA	Energy Research and Development Administration
		ESD	Environmental Sciences Division
		ESRC	Environmental Science Research Center
		EST	expressed sequence tag

Acronym	Expanded Name
EXAFS	extended x-ray absorption fine structure
FACE	Free Air Carbon Dioxide Field Enrichment
FAO	Food & Agricultural Organization (United Nations)
FCCSET	Federal Coordinating Council for Science, Engineering, and Technology
FCM	flow cytometry
FEM-PBL	Finite Element Method/Planetary Boundary Layer
Fermilab	Fermi National Accelerator Laboratory
FFF	field-flow fractionation
FFT	fast Fourier transform
FIRE	First ISCCP Regional Experiment
FISH	fluorescence in-situ hybridization
FLM	Free-Lagrange Method
FTE	full-time equivalent
FTIR	Fourier transform infrared
FTS	full turbulence simulation
FWHM	full-width-at-half-maximum
FWP	Field Work Proposal
GABA	gamma aminobutyric acid
GAS	General Arctic Simulator
GC	gas chromatography
GCM	global climate model
GCM	general circulation model
GC/MS	gas chromatography/mass spectrophotometer
GCRP	Global Change Research Program
GDB	Genome Database
GEM-HEX	Geochemical, Microbiological, Hydrological Experiment
GENLEAF	generic models of leaf response
GIS	Geographical Information System
GISS	Goddard Institute for Space Studies
GL	Geophysics Laboratory
GNP	gross national product
HASP	High Altitude Sampling Program
HBCU	Historically Black Colleges and Universities
HEHF	Hanford Environmental Health Foundation
HFBR	High Flux Beam Reactor

Acronym	Expanded Name
HGCC	Human Genome Coordinating Committee
HGI	Human Genome Initiative
HGIR	Human Genome Information Resources
HGMIS	Human Genome Management Information System
HOML	Human Gene Mapping Library
HGP	Human Genome Program
HGPRT	hypoxanthine-guanine phosphoribosyl transferase
HMEC	human mammary epithelial cells
HRIS	high resolution infrared spectrometer
HBP	hepatic binding protein
HPCE	high performance capillary electrophoresis
HPLC	high performance liquid chromatography
HPRT	hypoxanthine phosphoribosyl transferase
HSEF	hit size effectiveness function
hsp 70	heat shock protein 70
IAEA	International Atomic Energy Agency
IASC	International Arctic Science Committee
ICRCCM	Intercomparison of Radiation Codes in Climate Models
ICRP	International Council for Radiation Protection
ICSU	International Council of Scientific Unions
IDSS	Integrated Data Sounding System
IGBP	International Geosphere Biosphere Program
IIIP	International Intercalibration and Intercomparison Program (for Radon, Thoron, and Daughters Measuring Equipment)
ILB	initial lung burden
IM	ion microscopy
IMPDH	inosine 5'-monophosphate dehydrogenase
INEL	Idaho National Engineering Laboratory
IPCC	Intergovernmental Panel on Climate Change
IPCC/RSWG/EIS	Intergovernmental Panel on Climate Change/Response Strategies Working Group/Energy and Industry Subgroup
IR	infrared

Acronym	Expanded Name
ISCCP	International Satellite Cloud Climatology Project
ISEB 10	Tenth International Symposium on Environmental Biogeochemistry
ISS	integrated sounding system
ITRI	Inhalation Toxicology Research Institute
JCCCNRS	Joint Coordinating Committee on Civilian Nuclear Reactor Safety
JGOFS	Joint Global Ocean Flux Study
kbp	kilobase pair
KBS	K-edge subtraction
LAMPF	Los Alamos Meson Physics Facility
LANL	Los Alamos National Laboratory
LANSCE	Los Alamos Neutron Scattering Center
LARIS	Laser Atomization Resonance Ionization Spectroscopy
LBERI	Lovelace Biomedical and Environmental Research Institute
LBL	Lawrence Berkeley Laboratory
LDGO	Lamont-Doherty Geological Observatory
LDL	low density lipoprotein
LBS	large eddy simulation
LET	linear energy transfer
LIDAR	laser radar
LIF	laser-induced fluorescence
LIMS	laboratory information management system
LIRAD	laser radar-radiometer
LLE	low level exposure
LLNL	Lawrence Livermore National Laboratory
LMDS	locally multiply damaged sites
LMGS	ligation-mediated genomic sequencing
LOR	low reiteration (sequences)
LPAS	laser photoacoustic spectroscopy
MAB	monoclonal antibodies
MAC	macronucleus
MAD	multiwavelength anomalous diffraction
MAS	multiaperature sensor
MATS	Mesoscale Atmospheric Transport Studies
Mb	myoglobin
MECT	multiple energy computed tomography

Acronym	Expanded Name
MEG	magnetoencephalography
MBM	Molecular Exciton Microscopy
MER	medium reiteration (sequences)
MFRS	moderator filter reflector shielding
MGMT	O ₆ -methylguanine-DNA methyl transferase
MIBK	methyl isobutyl ketone
ML	myeloid leukemia
MM	mesoscale model
MNNO	n-methyl-n'-nitro-nitroguanidine
MoAb	monoclonal antibodies
MORACC	modeling radiation, clouds, and convection
MPC	massively parallel computer
MPO	N-methylpurinc DNA glycosylase
MQHPT	multiquantum, heteronuclear polarization transfer
MRI	magnetic resonance images (or imaging)
MS	mass spectrometry
MSRC	Molecular Science Research Center
MSU	microwave sounding unit
MURF	multiregion flow
MURT	multiregion transport
NADP/NTN	National Atmospheric Deposition Program/National Trends Network
NAPAP	National Acid Precipitation Assessment Program
NASA	National Aeronautics and Space Administration
NBRF	National Biomedical Research Foundation
NCAR	National Center for Atmospheric Research
NCBT	neutron capture boron therapy
NCRP	National Council for Radiation Protection
NCT	neutron capture therapy
NER	nucleotide excision repair
NERSC	National Energy Research Supercomputer Center
nf-EBM	noise-forced energy balanced models
NIGEC	National Institute of Global Environmental Change
NIH	National Institutes of Health

Acronym	Expanded Name
NIM	Nuclear Instrument Module
NINDS	National Institute of Neurological Diseases and Stroke
NIST	National Institute of Standards and Technology
NLGLP	National Laboratory Gene Library Project
NMR	nuclear magnetic resonance
NOAA	National Oceanic and Atmospheric Administration
NSF	National Science Foundation
NSLS	National Synchrotron Light Source
NTA	nitriloacetic acid
OGCM	Ocean General Circulation Model
OMIM	online <i>Mendelian Inheritance in Man</i>
OMP	Ocean Margins Program
ORNL	Oak Ridge National Laboratory
ONR	Office of Naval Research
OS	open systems
PA	plasminogen activators
PACE	pulse alternating current electrophoresis
PAF	platelet activating factor
PAH	polycyclic aromatic hydrocarbons
PAL	photoaffinity labels
PAR	photosynthetically active radiation
PAT	photon activation therapy
PBL	Planetary Boundary Layer
PCC	premature chromosome condensation
PCCS	physicochemical carcinogen-screening
PCMDI	Program for Climate Model Diagnosis and Intercomparison
PCNA	proliferating cell nuclear antigen
PCR	polymerase chain reaction
PDB	Protein Data Bank
PDL	polarization diversity lidar
PDS	photothermal deflection spectroscopy
PER	Program for Ecosystem Research
PET	positron emission tomography
PFT	perfluorocarbon tracers
PICL	portable instrumented communications library
PIR	protein identification resource
PIV	particle image velocimetry

Acronym	Expanded Name
PLFA	phospholipid ester-linked fatty acid
PNA	polynuclear aromatic
PNL	Pacific Northwest Laboratory
PSV	particle streak velocimetry
PUREX	plutonium-uranium extraction process
PVDF	polyvinylidene difluoride
QARG	quantitative autoradiography
R4D	Response, Resistance, and Resilience to and Recovery from Disturbance
R6G	rhodamine 6G
RADCAL	Radiation Calibration Laboratory
RAMP	Remote Atmospheric Measurements Program
RAMS	Remote Atmospheric Measurements Systems
RASS	Radio Acoustic Sounding System
RB	replication band
Rb	retinoblastoma
RBE	relative biological effectiveness
RB-RNAP	ribonucleic acid polymerase labeled with rose bengal
rCBF	regional cerebral blood flow
REMPI	resonance-enhanced multiphoton ionization
REV	representative elementary volumes
RFLP	restriction fragment length polymorphism
RFS	remote fiber spectroscopy
RH	relative humidity
RIDIC	Radiopharmaceutical Internal Dose Information Center
RIMS	resonance ionization mass spectrometry
RIS	resonance ionization spectroscopy
RIT	radioimmunotherapy
RSR	rotating shadowband radiometer
RT	radiative transfer
SABLE	simulator atmospheric boundary layer environment
SAGE	stratospheric aerosol and gas experiment
SAIC	Science Applications International Corporation
SASP	Surface Air Sampling Program
SBC	Structural Biology Center
SBH	sequencing by hybridization

Acronym	Expanded Name	Acronym	Expanded Name
SCAR	Scientific Committee on Antarctic Research	TEC	tracheal epithelial cells
SCE	sister chromatid exchanges	TeraFLOP	trillion floating point operations per second
SEEP	shelf edge exchange processes	THG	third harmonic generation
SEOM	scanning excitation optical microscopy	TMC	Thinking Machines Corporation
SERF	Subsurface Environmental Research Facility	TOF	time-of-flight
SERS	stimulated electronic Raman scattering or surface-enhanced Raman spectroscopy	TOGA	Tropical Ocean-Global Atmospheric
SIRIS	Sputter-Initiated Resonance Ionization Spectroscopy	TRITC	tetramethylrhodamine isothiocyanate
SMCC	Subsurface Microbial Culture Collection	TUT	thiouracil therapy
SMMR	scanning multichannel microwave radiometer	UCAR	University Corporation for Atmospheric Research
SORTI	Solar Radiance Transmission Interferometer	UCSF	University of California at San Francisco
SPECT	single-photon emission computed tomography	UNM	University of New Mexico
SPECTRE	Spectral Radiance Experiment	USGCRP	U.S. Global Change Research Program
SQUID	superconducting quantum interference devices	UVA	ultraviolet "A"
SREL	Savannah River Ecology Laboratory	UVR	ultraviolet radiation
SRS	Savannah River Site	UW/UD	University of Wisconsin/University of Denver
SSP	Subsurface Science Program	VEI	volcano explosivity index
SST	sea surface temperature	VLSI	very large scale integration
STARS	steady-state transport of air and radon in soils	VPSAM	variable pathlength spectral attenuation meter
stDNA	satellite DNA	VVP	vertical ventpipes
STEM	scanning transmission electron microscopy	VUV	vacuum ultraviolet
STM	scanning tunneling microscopy	WCRP	World Climate Research Program
STS	sequence-tagged site	WGGC	Working Group on Global Change
SUPF	suppressor function	WHHL	Watanabe heritable hyperlipidemia
TCA	Tandem Cascade Accelerator	WIND	weather information display
TCE	trichloroethylene	WOCE	World Ocean Circulation Experiment
TE	tracheal epithelium	WOCE/HP	World Ocean Circulation Experiment—Hydrographic Program
		XP	xeroderma pigmentosum
		YAC	yeast artificial chromosome

Summaries of FY 1992 Research Sponsored by the Office of Health and Environmental Research

Health Research

Radiation and Chemical Effects: Biological Effects Studies

Intramural DOE Laboratories

Argonne National Laboratory Argonne, IL 60439

Biological and Medical Research Division

001. Biochemical Mechanisms of Chemically Induced Health Effects

M.H. Bhattacharyya
(708) 972-3923

\$100,000

This project's goals are to better understand the adverse human health effects of chemicals produced as byproducts of developing energy technologies and to develop and evaluate approaches for early detection of low level exposures and responses. The program develops techniques to analyze human blood as a measure of exposure to environmental levels of energy-related chemicals. Organ and cell culture systems are used to study bone demineralization shown to result from exposure to low levels of cadmium, especially in females during pregnancy, lactation, and menopause. Current studies are focused on (1) characterizing the biochemical pathways that lead to toxic responses to metals; (2) identifying the mechanism(s) underlying metal-induced bone demineralization; and (3) studying the role of lactation-induced increases in the metal-binding protein, metallothionein. The recent development of a highly sensitive assay for blood cadmium by this project now enables researchers to determine whether releases of metals from waste sites result in increased exposure to residents living nearby. (RPIS 3439)

002. Interspecies Extrapolation for Radiation-Induced Carcinogenic Risk

B.A. Carnes
(708) 252-3819

\$100,000

This program characterizes and quantitates the relationship between external exposure (quality, amount, rate, or pattern of exposure) to radiation, potential confounders (sex, age,

species), and the pathologic conditions observed at death, by using comparative lifetable analyses and failure time models. This project entails (1) collecting survival data for a variety of species, (2) organizing the data under a single data management system, and (3) investigating the lifetable and characterizing the dose response within species by using a common analysis paradigm. The placement of data from several species under a unified data management and analysis structure facilitates interspecies comparisons and permits the development of models capable of predicting neoplastic risks across species boundaries (e.g., mouse to man). (RPIS 5524)

003. Radiation Toxicity Studies in Dogs for Interspecies Comparison

T.E. Fritz
(708) 972-3814

\$100,000

This program provides information on the late effects of ionizing radiation in a large, relatively long-lived animal, the dog. The information is used to develop extrapolation models that will relate the data available from short-lived laboratory species to humans. The specific objectives are to (1) determine the relative influence of two major factors, daily dose rate and total accumulated dose, on biological damage; (2) provide data for estimates of radiation-specific excess mortality rates in dogs to enable interspecies comparisons with existing rodent data; and (3) study radiation damage in relation to life shortening and death, with particular emphasis on leukemia and other pathology of the blood-forming system. Adult beagles are exposed to protracted whole-body ^{60}Co γ irradiation for 22 hours a day, 7 days a week. They are given various dose rates down to those that allow a nearly normal life span, either until death or until predetermined total doses are accumulated. Earlier studies showed that (1) the mortality rate for the dog, as for the mouse, is determined by the dose rate over the range of doses that results in 50 percent life shortening, and (2) death usually results from damage to the blood-forming system (primarily the bone marrow). However, the hematopoietic system in some dogs can adjust to continuing irradiation, so that the longest survivors die of other causes. The studies determine whether dogs, which are more sensitive to high dose rates of irradiation than small laboratory rodents, are less sensitive at lower dose rates. These studies also establish the target organs and causes of death at the lower dose rates and determine whether, as in rodents, the life shortening depends on total dose rather than

dose rate. These studies may also help to establish whether information from small, short-lived rodents can be used to predict health effects in humans and to help set radiation standards for human exposure. These findings are important in developing a unified concept of radiation damage. (RPIS 0109)

004. Analysis of Protein Expression

C.S. Giometti

(708) 972-3839

\$600,000

Two-dimensional gel electrophoresis (2DE) can be used to separate protein mixtures into patterns containing hundreds of distinct protein subunits, each with a characteristic isoelectric point and molecular weight. Coupled with computerized image and data analysis, the 2DE technique used to detect quantitative changes in protein expression and positional or presence/absence differences. This project uses 2DE to detect changes in protein patterns that correlate with exposure of a biological system to chemicals or ionizing radiation. Mouse mutagenesis studies are designed to demonstrate the types and frequency of heritable mutations that can be detected by 2DE. Thus far, the project has detected five positional variants in the protein patterns from offspring of ethyl nitrosourea-treated male mice and two quantitative variants in patterns from offspring of male mice exposed to fission spectrum neutrons. (One of these two events occurred in two littermates and has been traced to the untreated dam rather than the exposed sire.) These data demonstrate that 2DE can be used to detect mutation events that cause only quantitative changes in the 2DE pattern (e.g., deletion of one copy of a gene), and can also detect events that cause the appearance or disappearance of proteins. Chemical toxicology studies are designed to define patterns of protein expression that may serve as indicators of exposure events. Analysis of liver proteins from mice exposed to four different chemicals known to cause peroxisome proliferation (and subsequent hepatocellular carcinoma) has shown that both common and specific effects are detectable. Data from animals treated with other agents that cause known biological effects in the liver will indicate which proteins are indicators of general tissue damage and which are involved in more specific responses (e.g., hepatomegaly-related protein patterns versus detoxification-related protein patterns). Analysis of protein patterns from blood cells and tissue culture systems allows extension of these studies to include human samples. Therefore, in both the mutagenesis and toxicological studies, the ultimate goal is to apply the 2DE technology to monitor human samples for changes in protein patterns that indicate exposure events. (RPIS 2454)

005. Mutagenesis and Carcinogenesis by Low Dose Irradiation

D.J. Grdina

(708) 972-4235

\$766,000

This program focuses on radiation-induced mutagenesis and carcinogenesis and associated mechanisms of action in C₃H and B6CF₁ mice, and selected in vitro repair-proficient and

-deficient cell systems. Its goal is to better assess and protect against radiation hazards in humans. Animals that were irradiated with single or fractionated exposures of 0.85-MeV fission neutrons or ⁶⁰Co gamma-rays, were observed for either defined periods of time or their lifetimes to ascertain mutation and/or cancer induction. When required, causes of death were determined by gross and microscopic examination of decedents; dose-response curves are being developed. Protracted exposure to neutrons increases life-shortening and associated tumor pathology as compared with single neutron doses of the same magnitude. Below 60 cGy, the life-shortening response following neutron exposure is linear and not influenced by protraction. The relative effectiveness of neutrons over gamma-rays varies between 3 and ~50, depending on total dose, dose range, dose rate, and cause of death. Neutrons are more efficient in the induction of epithelial tissue tumors, whereas gamma-rays are more effective in the induction of connective tissue tumors. Amino-thiol compounds, specifically S-2-(3-aminopropylamino)-ethylphosphorothioic acid (WR2721) and S-3-(3-methylaminopropylamino)-propylphosphorothioic acid (WR151327) protect against neutron- and gamma-ray-induced life shortening, tumor formation, and mutagenesis. These data are being evaluated and compared to appropriate elements of the JANUS mouse-life-shortening database. Genotoxic endpoints are investigated by using both in vivo and in vitro systems. The mutation assay is directed at the hypoxanthine-guanine phosphoribosyl transferase locus. Deoxy ribonucleic acid (DNA) damage and repair are also routinely measured in both in vivo and in vitro experimental systems, and agents that can modify radiation damage are used as probes to modulate and study associated processes leading to mutagenesis and carcinogenesis. (RPIS 0101)

006. Chemical Carcinogenesis Studies in Human and Rodent Cells

E. Huberman

(708) 972-3819

\$500,000

This research, using cultured human and rodent cells, studies the cellular and molecular events that govern tumor promotion and progression in chemical- or radiation-induced carcinogenesis. Previous research led to the development of cell culture systems and specific probes for such investigations. Current studies involve two major types of experiments. In the first type, tumor-promoters such as phorbol 12-myristate 13-acetate and okadaic acid and related agents are tested for their ability to initiate early biochemical events (e.g., activation of protein kinase, protein phosphorylation) that cause alterations in gene expression leading to modulation of cell differentiation. These events are analyzed in human cells that are either susceptible or resistant to the induction of cell differentiation by these tumor promoters. Differentiation is characterized by changes in morphological patterns, functional molecules, enzymatic markers, and reactivity with monoclonal antibodies. Alterations in the expression of specific genes are detected through recombinant DNA techniques with well-defined cDNA probes. In the second type of

experiments, inosine 5'-monophosphate dehydrogenase (IMPDH), an enzyme associated with growth progression in tumor cells, is examined for its involvement in the control of growth and differentiation in normal and malignant human cells. Growth and the induction of differentiation is suppressed by treating the cells with enzyme inhibitors. IMPDH gene expression is modulated by using specific inhibitors and enzyme products; modulation is detected with IMPDH DNA probes and monoclonal antibodies that have been developed and characterized. These studies should allow identification of critical cellular and biochemical events involved in carcinogenesis, cell growth, and differentiation. The studies also broaden the spectrum and sensitivity of cell culture systems used to identify and study potential carcinogens, tumor progressors, and tumor promoters. (RPIS 4190)

007. Oncogenes and Human Radiation Carcinogenesis

E. Huberman

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\$350,000

The project objective is to obtain basic information on the role of internally deposited alpha-particle-emitting radionuclides in the development of cancer in humans. Normal and malignant tissue from subjects at low and high risk of developing radiation-induced cancers is used to study the critical molecular events that underlie the carcinogenic process. The focus is on the identification of changes in proto-oncogene and tumor suppressor gene structure and expression. Tissues (most of them "normal") from human subjects with internal exposure to radium are analyzed. A fraction of these tissues contain alterations in the structure of the *c-mos* proto-oncogene. No such alterations are detected in tissues from age-matched control subjects, nor are related alterations found in the structure of other proto-oncogenes from the control or exposed subjects. Also, research shows that subjects exposed to this carcinogen have deletions and alterations in the retinoblastoma (Rb) gene, a tumor suppressor gene. More studies characterize the nature of the alterations in the *c-mos* and Rb genes as well as other tumor-controlling genes. Such analysis extends to tissues from other radium-exposed humans. Tissues obtained from individuals exposed to other alpha-particle-emitting radionuclides are also analyzed. In one such case, blood DNA samples from a subject injected with the radioactive compound Thorotrast demonstrated a deletion in the *c-fms* proto-oncogene. Alterations at the *c-fms* locus are associated with the development of myeloid leukemia, a type of cancer frequently observed in Thorotrast cases. Tissues from radium- and related radionuclide-exposed human subjects provide a unique resource for studies on the role of specific tumor-controlling genes in human radiation carcinogenesis. (RPIS 4581)

008. Radiation-Induced Changes in Mammalian Cells

J.L. Schwartz

(708) 972-3919

\$200,000

This research program investigates the action of different types of ionizing radiation on defined biological processes in cultured cells. The program focuses on types of ionizing radiation related to the development of carcinogenesis in humans. The information gained in these studies provides guidance for developing models of radiation carcinogenesis. The studies examine the effects of exposure to ionizing radiation in mammalian cells in vitro at the level of the gene, DNA, chromosome, and cell. In addition, the influence of various physical and biological factors such as dose, dose rate, radiation quality, inherent repair, and genetic locus are investigated. The principal line of investigation concerns fission-spectrum neutron effects. The efficiency with which fission-spectrum neutrons can induce certain kinds of biological damage (e.g., cell transformation, mutagenesis, and life shortening) is increased by protraction or fractionation of the dose. Elucidation of the mechanisms underlying the dose rate relationship is sought by focusing on the molecular events produced by neutrons at different dose rates and the influence of DNA repair. Knowledge of the lesions induced, the cellular processing of these lesions (which may be involved in carcinogenesis), and the modifying influence of various physical and cellular factors contributes to development of dosimetric models of risk estimation. (RPIS 1297)

009. Analysis of DNA Damage and Mutation Induced by Radon Daughter Products

J.L. Schwartz

(708) 972-3919

\$265,000

This program examines the effects of radon exposure on mammalian cells at the level of gene, DNA, chromosome, and intact cell. It also compares the responses to radon exposure of cell lines with different radiation sensitivities and different abilities to repair DNA damage. Initial studies focused on four Chinese hamster ovary cell lines (AA8, EM9, CHO-K1, and xrs-5), which differ in radiation sensitivity and in their ability to repair DNA strand breaks. By comparing the responses of these cell lines to radon daughter exposure, i.e., gene mutation induction (quantity and quality), DNA strand-break induction and rejoining, chromosome aberration induction, and cell killing, researchers can learn about the importance of specific types of DNA damage in radon-mediated events, as well as the modifying effects of different repair backgrounds. One new direction resulting from the initial studies is an investigation of the importance of cell cycle changes in radiation-induced effects. The long-term goal is to use molecular, biochemical, cytogenetic, and cellular assays of DNA damage induction and repair to help us understand (1) the nature of the lesions induced by radon and (2) how they become mutagenic and carcinogenic. (RPIS 5354)

010. Hematopoiesis in Chronic Toxicity Studies*T.M. Seed*

(708) 972-3865

\$300,000

Aplastic anemia and myelogenous leukemia are, under select conditions, prominent pathological consequences of exposure to ionizing radiation. This project seeks to elucidate the cellular and molecular mechanisms by which chronic exposure to ionizing radiation induces and promotes the development of these major hematologic pathologies. Whole animals (previously beagle dogs, currently CBA mice), as well as surrogate bone marrow organ cultures, are exposed daily to low doses of ^{60}Co gamma irradiation, to study the sequential changes in the blood-forming system during the prepatent stages of aplastic anemia and myelogenous leukemia. Emphasis is placed on the structural and functional properties of the blood-forming stem cells, the suspected cellular targets for the radiation-induced effects. Specific preclinical stages and events for each syndrome have been identified and partially characterized. Aberrant hematopoietic recovery is a pivotal, early occurring stage that precedes eventual development of either aplastic anemia or myelogenous leukemia. This recovery is associated with an acquired increase in radioresistance of selected subpopulations of targeted hematopoietic stem cells with altered cell-cycle and proliferative properties. The magnitude of the acquired radioresistance appears to be directly related to the daily rate of exposure and, in turn, to the overall myeloid leukemic incidence. Nonrandom chromosomal changes and altered cellular repair patterns are temporally associated with the change in radiosensitivity and may provide the basis for hematopoietic recovery. This project's goals are to confirm these associations, originally developed using canines, in a second species (rodents) and to extend understanding of underlying genetic and molecular bases of the acquired stem cell functions that predispose irradiated individuals to either aplastic anemia or myelogenous leukemia. Characterization of the predisposing factors of chronic radiation-induced pathogenesis will permit development of criteria for early diagnosis and prognosis in humans and development of preventive measures. (RPIS 2759)

011. Genetic Effects of High Linear Energy Transfer Radiation*G.E. Woloschak*

(708) 972-3312

\$220,000

This project's goal is to study the modulation of gene expression that occurs both in vitro (Syrian hamster embryo cells) and in vivo (mouse) following exposure to ionizing radiations. Experiments are designed for the following purposes: (1) to identify changes in gene transcription induced immediately following exposure of cells to neutrons, (2) to compare changes induced by high linear energy transfer (LET) neutrons to those produced by low LET radiations (such as x-rays and gamma-rays), and (3) to determine the role that these transcriptional changes play in cell survival and DNA repair. In the cell culture systems, several genes have been identified that are modulated

by both high and low LET radiations. A series of genes has been identified that are modulated similarly following exposure to JANUS neutrons and gamma-rays, and another set of genes that are modulated differently following exposure to different qualities of radiation. For each of these gene modulations, the effects of dose, dose rate, and stage of the cell cycle, as well as the kinetics and mechanisms of gene modulation, are pursued. In addition, work is done using in vivo radiation exposures to determine whether in vitro gene modulation events are evident in whole animals as well. This work so far has demonstrated that many of these events evident in cells following radiation exposure can be attributed to gene-specific transcriptional changes. The mechanisms responsible for the transcriptional events, however, are not clearly understood. Work with repair-deficient wasted mice has shown repression of *c-fos* to be delayed relative to repression in control mice. In addition, total transcription is induced in repair-deficient mice (rather than repressed as occurs in controls) following whole-body JANUS neutron exposure. This work enhances understanding of the molecular response to ionizing radiations of different qualities. (RPIS 0107)

012. Inactivation of Cancer Suppressor Genes in Radiation-Induced Tumors*G.E. Woloschak*

(708) 972-3312

\$299,000

It is now known that human retinoblastoma, the majority of human osteosarcomas, and some breast and lung cancers are associated with the functional loss or inactivation of a specific gene located at chromosomal location 13q14.2. This retinoblastoma gene (*Rb-1*) is believed to be a dominant cancer suppressor gene. Thus, the *Rb-1* locus is of special significance in the study of radiation-induced tumors because radiation is known to be a potent clastogenic agent, producing primarily deletion-type mutations. Other tumor suppressor genes such as *p53* may also be appropriate subjects for study. This project's goal is to determine the potential role of the cancer suppressor genes (such as *p53* and *mRb*) in radiation-induced osteosarcomas and in other radiation-induced tumors such as liver and lung cancer and leukemias. A number of radiation-induced tumors are available in the Argonne National Laboratory (ANL) tissue repository from JANUS fission-spectrum neutron and gamma-ray exposure, as well as spontaneously arising tumors. Tissue from tumor samples is used to determine the frequency and types of alterations that occur in cancer suppressor genes and to examine expression of the gene by in situ hybridization as well as Western blot binding studies. Preliminary studies using sensitive polymerase chain reactions technology demonstrate the ability to detect *mRb* lesions in paraffin-embedded samples of spontaneous liver and lung tumors from BCF mice that were part of the ANL and JANUS neutron/gamma-ray studies. These studies allow researchers to begin to define the molecular events involved in radiation-mediated carcinogenesis. (RPIS 5353)

Brookhaven National Laboratory Upton, NY 11973

Medical Division

013. Radiation Carcinogenesis—Dose-Effect Relationships of Varying Energies of Neutrons in Leukemogenesis

V.P. Bond

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\$290,000

The research objective is to develop for myeloid leukemia (ML) the "hit size effectiveness function" (HSEF), which provides the probability of malignant cell transformation as a function of the amount of energy transfer per cell. To accomplish this aim, mice are exposed to small amounts of low linear energy transfer (LET) radiation and different monoenergetic fast neutron beams, from which quantitative macro- and microdosimetric data are obtained. HSEF, with microdosimetric data on the frequency of hits and distribution of cell doses from low level exposure (LLE), permits researchers to obtain quickly and easily the risk of cancer after exposure to radiation of any one quality or to an admixture. In principle, the approach obviates the need for relative biological effectiveness, Q, and dose equivalent. Because myelocytic leukemia in humans is single cell in origin, researchers can presume that each leukemia is a marker for a fully transformed cell. Thus, this is the first and only study that deals with a cancer at the cellular level, with respect to the microdosimetric aspects (the number of cells affected and the distribution of energy transfers), but also with the result in terms of the fraction of quantal responders. Cytogenetic and molecular evaluation of ML cells will provide information on the possible association of a specific chromosomal change or oncogene activation with ML. Cellular control of in vitro progression of ML cells in the presence or absence of growth factors demonstrates the capability of autocrine secretions of ML cells. At intervals after irradiation, karyotyping, hematology, and histology are used to determine the potential role of a specific chromosomal abnormality and the development of leukemia. (RPIS 4857)

014. DNA Repair, Cytogenetics, and Epidemiology

R.B. Setlow

M.A. Bender

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\$280,000

An important role in evaluating the effects of radiations and fuel-derived environmental mutagens and carcinogens on humans must be played by the distribution of responses among exposed individuals. From the analysis of DNA repair-deficient human diseases, it is known that there are very small supersensitive subsets. This very restricted number of supersensitive individuals is not an important public health problem, but the existence of large numbers of individuals several-fold more sensitive than the average would be an important one.

Are there such sensitive subsets in the population and, if so, how large are they? The answers to these questions are important in setting standards for exposure levels and for extrapolating from limited epidemiological studies to the entire population. A way to enlarge the epidemiological database is to measure the cytogenetic and DNA-repair responses of cells from a representative cross section of the population. Preliminary measurements indicate large differences in repair abilities among individuals as measured by (1) the responses of lymphocytes exposed to ultraviolet (UV) radiation in vitro, (2) the abilities of lymphocyte extracts to remove O⁶-methylguanine from alkylated DNA, and (3) the cytotoxic effects of x rays or N-methyl-N' nitro-N-nitrosoguanidine (MNNG) on fibroblasts. These studies include the effects of UV, x rays, MNNG, and mitomycin C on lymphocyte cultures derived from several hundred members at Brookhaven National Laboratory. The endpoints will include unscheduled DNA synthesis, sister chromatid exchanges, formation of micronuclei, and m¹C methyltransferase activity. (RPIS 3787)

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Laboratory for Radiobiology and Environmental Health

015. Mechanisms of Mutagenesis by Alpha Particles and X Rays in Human Cells

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\$130,000

Alpha particles are a densely ionizing form of radiation with a high relative biological effectiveness. Nevertheless, cells can survive the passage of multiple alpha particles through their nuclei, if the track lengths are short, with production of a range of mutations. A shuttle vector system suitable for the study of mutagenesis from ionizing radiation with emphasis on detection of deletions produced by x rays and radon alpha particles is under development. This shuttle vector is carried as extra-chromosomal episomes, up to 100 copies per cell, in human lymphoblastoid cells from normal donors and from patients with ataxiatelangiectasia and xeroderma pigmentosum. The shuttle vector is 10.3 kb in size and permits detection of point mutations in a target gene of 3.1 kb and of deletions up to 8.5 kb in size. DNA sequence analysis of deletion junctions provides information about molecular mechanisms of rejoining of double-strand breaks. (RPIS 5013)

016. Elucidation of Cytogenetic Damage*S. Wolff**W.F. Morgan**(415) 476-1636**\$650,000*

Mutagenic carcinogens that break chromosomes, produce sister chromatid exchanges, and induce mutations are released during the production of energy from almost all sources. These physical or chemical contaminants can have severely detrimental biological effects. They can induce cancer or sterility in the individuals exposed or can lead to heritable detrimental mutations that can affect future generations. Because researchers have an incomplete understanding of the biophysical and biochemical processes involved in the induction of genetic damage by these substances, they are unable to reverse it. Therefore, to gain a better understanding of the biological hazards associated with energy production and to help cope with these hazards, researchers in the cytogenetics program are attempting to characterize the initial lesions that produce genetic effects and to understand the biological repair processes that modify the lesions. Because the structure of the eukaryotic chromosome is still not completely known, experiments are being conducted to obtain a basic understanding of chromosome structure, function, exchange formation, and the biochemistry of replication in order to elucidate the mechanisms involved in the induction of chromosome aberrations and sister chromatid exchanges by mutagenic carcinogens. The experiments are carried out with mammalian cells, including human cells, in culture. (RPIS 0218)

Inhalation Toxicology Research Institute
 Albuquerque, NM 87185
017. Influence of Modifying Factors on Metabolic Fate of Inhaled Organic Compounds*W.E. Bechtold**(505) 845-1904**\$150,000*

This project's objective is to develop information that will provide insights into exposure-effective dose response relationships for inhaled toxicants. These researchers identify specific damage to DNA from inhaled toxicants that can potentially lead to mutation and characterize the ability of tissues to repair the damaged DNA. When possible, specific cell types, as well as organ systems, are being characterized in regard to adduct formation and repair. Concurrent studies involve development and characterization of new biological markers of exposure (e.g., urinary metabolites, hemoglobin adducts, and serum albumin adducts) to inhaled toxicants. These biomarkers serve as more precise measures of internal dose of the inhaled chemicals. The goal of developing these methods is to predict exposure-effective dose relationships for humans and identify human populations at risk in both environmental and occupational settings. (RPIS 4497(A))

018. Mechanisms of Chemically Induced Carcinogenicity*S.A. Belinsky**(505) 845-8681**\$566,000*

The purpose of this project is to investigate mechanisms of chemically induced carcinogenicity in the respiratory tract following chronic exposure to complex mixtures or specific environmental carcinogens. This approach uses both in vivo and in vitro studies and relies heavily on techniques in the disciplines of molecular biology, cell biology, biochemistry, and pathology. F344 rats are exposed to diesel exhaust or to carbon black, an inert particle analogue, in a lifespan study. This carcinogenicity study determines the role of soot-associated organic compounds in pulmonary neoplasia associated with exposure to diesel exhaust. Preliminary results indicate that carbon black does produce tumors in the F344 rat and that the incidence is similar to that observed with diesel exhaust. These results suggest that the organic carcinogens present in diesel exhaust may not be involved in cell initiation and progression to neoplasia. Ongoing studies examine the role of cell proliferation in the development of hyperplastic foci produced during exposure to diesel exhaust. In addition, the relationship between clearance and retention of lipophilic compounds within the lung to the development of lung cancer is being investigated. Future research will concentrate on identifying the target genes and cells for chemically induced lung tumors, defining the time course for activation of transforming genes and inactivation of tumor-suppressor genes during the development of cancer, and identifying factors involved in the progression of pulmonary neoplasia. These studies will examine the molecular mechanisms involved in the induction of pulmonary neoplasia by carbon black, diesel exhaust, cigarette smoke, and beryllium. By comparing results obtained from studies on these complex mixtures and chemicals, researchers can identify common pathways involved in tumor formation. This knowledge should improve the basis for predicting the health risk to humans from exposure to environmental carcinogens. (RPIS 4498)

019. Role of Immune Responses in Respiratory Diseases*D.E. Bice**(505) 845-1406**\$300,000*

The project hypothesis is that alterations in lung and airway immune responses following inhalation of toxicants can lead to lung diseases. The interactions of inhaled pollutants with pulmonary immune defenses could decrease pulmonary immunity, resulting in increased lung infections or possibly cancer. However, it is also possible that inhalation of pollutants may increase the incidence of immunity to inhaled chemicals or environmental allergens, leading to pulmonary hypersensitivity. The approach to test this hypothesis is to identify the mechanisms responsible for normal pulmonary immune responses that are essential for protecting the lung against infectious organisms or tumor growth and to then determine

how inhalation of toxicants may alter normal defenses and cause lung disease. People living in highly polluted communities experience increased pulmonary infections; this suggests that their pulmonary immune defenses may have been damaged by inhaled pollutants. However, the incidence of pulmonary hypersensitivity has always been relatively high, and epidemiology data indicate that the incidence and severity of asthma, as well as mortality due to asthma, have significantly increased. The researchers study possible suppressive effects of inhaled toxicants, expanding research to determine how inhalation exposures may lead to increased pulmonary hypersensitivity. (RPIS 4499(A))

020. Toxicity of Injected Actinides

B.B. Boecker

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\$800,000

A lifespan study of the comparative radiotoxicity of intravenously injected ^{239}Pu and ^{226}Ra in beagle dogs was initiated at the University of Utah in 1952 to estimate the human health risks from internally deposited ^{239}Pu , compared to the known effects of ^{226}Ra in humans. Lifespan toxicity studies involving other radionuclides (^{90}Sr , ^{228}Ra , ^{228}Th , ^{241}Am , ^{244}Cf , ^{252}Cf , ^{252}Es , and ^{226}Ra) began in later years, for comparison with the results for ^{239}Pu and ^{226}Ra . There are now 11 studies in which all dogs are dead and 3 studies in which one or more dogs remain alive. Continued care and follow-up of the dogs remaining alive is provided at the Inhalation Toxicology Research Institute (ITRI). This project supports (1) the housing, clinical care, and analyses of dogs moved to ITRI and involvement of ITRI and University of Utah personnel in completing and publishing the results of several of these studies; (2) efforts by scientists at the University of Utah to complete reviews and analyses of materials and data collected from past studies and publication of summary reports in the open scientific literature; and (3) studies of bone microdosimetry, especially for ^{239}Pu and ^{226}Ra . Items 2 and 3 and portions of item 1 are covered under a subcontract from ITRI to the University of Utah. These activities ensure orderly completion of the toxicity studies and maximize their value in assessing human health risks from internally deposited radionuclides, particularly those related to bone cancer. (RPIS 4976)

021. Influence of Respiratory Tract Metabolism on Effective Dose

A.R. Dahl

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\$100,000

This project investigates the metabolic fate of inhalants. It studies the contribution of respiratory tract enzymes to the metabolism of inhalants. It involves species comparisons of capabilities for handling inhalants, with emphasis on human capabilities. Specific aims are to determine (1) which enzymes metabolize inhalants in rats and humans and (2) the distribution of xenobiotic metabolizing enzymes at the tissue, cell, and organelle level within the respiratory tract. Also explored are ways to examine the role of metabolism in

olfaction. To accomplish these goals, techniques from molecular biology, neurobiology, analytical chemistry, and various subdisciplines of toxicology are used. (RPIS 4497(B))

022. Mechanisms of Granulomatous Disease from Inhaled Beryllium

G.L. Finch

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\$150,000

Beryllium is a unique metal that, because of its physicochemical properties, has found widespread use in the electronics, aerospace, and nuclear industries. Inhalation exposure to beryllium may result in chronic beryllium disease (CBD), a potentially fatal disease characterized predominantly by progressive, noncaseating granulomatous lesions of the lung. There is a concern of increased risk for CBD because of increasing use of beryllium compounds in advanced technology industries that include fabrication of components for various DOE programs. Beryllium-specific pulmonary immune responses in sensitive, beryllium-exposed individuals probably mediate CBD. However, the mechanisms and regulation of immune responses to inhaled beryllium are poorly understood. This research examines numerous issues that are of major concern for those exposed to beryllium compounds. The project investigates the relationship between toxicity and the physicochemical form of the beryllium to which an individual is exposed, as well as other exposure-related events. The molecular and cellular mechanisms of beryllium-specific immune responses within the lung and their relationship to ensuing granulomatous lung lesions are being examined. To accomplish this, a suitable laboratory animal has been identified for exposure by inhalation to well-characterized aerosols of beryllium compounds. (RPIS 4500)

023. Effective Dose from Inhaled Nuclear Energy Materials

R.A. Guilmette

(505) 845-5835

\$650,000

This research project focuses on three areas: (1) the measurement of the spatial and temporal distribution of radiation dose at the whole organ, suborgan, and microdosimetric level; (2) the elucidation of the mechanisms by which inhaled aerosols are cleared from or retained in the respiratory tract; and (3) the integration of knowledge and data from human exposure cases and experimental animal studies to develop improved biokinetic/dosimetric models needed for establishing exposure guidelines, interpreting human bioassay data, and calculating committed doses to organs at risk from inhaled radionuclides. Mechanistic studies focus on defining the functional roles of phagocytic cells of the respiratory tract. Results indicate that (1) species-related differences exist in the initial rates of uptake of particles by rat and dog alveolar macrophages and (2) significant differences exist in the relative distribution of particle-laden cells in the lung parenchyma, which may partially explain the observed differences in long-term retention of particles among species. Recent dosimetry results focused on human nasal airways have indicated magnetic

resonance imaging is an effective method for measuring nasal airway dimensions *in vivo*. Replica models of human nasal airways based on magnetic resonance imaging data are constructed using computer-assisted micromilling techniques, and deposition of well-characterized aerosols in the replica models is being measured both in terms of total and regional deposition patterns. Development of dosimetry models for the respiratory tract, based on the most recently acquired biokinetic and metabolic data, continues. National Council for Radiation Protection and International Council for Radiation Protection task groups also continue to redesign their respiratory tract dosimetry models. (RPIS 4492)

024. Links Between Radiation-Induced Lung Cancer in Laboratory Animals and Humans

F.F. Hahn

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\$250,000

The objective of this research is to clarify the dose-response relationships at lower doses (5-20 Gy) for inhaled low linear energy transfer emitters or external irradiation and cellular mechanisms affecting radiation-induced lung cancer in laboratory animals and to relate them to radiation-induced lung cancer in humans. The first objective is to test three hypotheses related to the extrapolation of dose-response data from studies with rats to human exposure situations. The three hypotheses are: (1) the risk of lung cancer in rats exposed to low, protracted beta irradiation of the lung is less than 50 tumors/10⁴ Gy, (2) the risk of lung cancer is higher with acute x-ray doses to the lung than with protracted beta irradiation, and (3) the risk of lung cancer in rats exposed to whole-body irradiation is similar to the risk observed in atomic bomb survivors. The second objective is to examine and quantify changes taking place in the lung before the appearance of frank neoplasia and assess their role in radiation-induced lung cancer. Specific questions are as follows: (1) What are the cells of origin for radiation-induced lung cancer in rats? (2) What are the cytokinetic and cellular proliferative changes induced by irradiation? (3) What role do these changes play in radiation pulmonary carcinogenesis? When life-span, dose-response studies with rats irradiated by x rays or internally deposited beta emitters are completed and results analyzed, the data are compared with the available data from exposed human populations. Short-term studies of cell proliferation and cytokinetics are performed to provide data for statistical models used to analyze the life-span, dose-response study results. Besides providing essential information for estimating the human health risks of pulmonary irradiation, these studies provide important information on the pathogenesis of lung cancer. (RPIS 4493)

025. Morphology of the Respiratory Tract and Response to Injury

J.R. Harkema

(505) 845-1005

\$320,000

Airway epithelial cells are often the first cells to be altered by inhaled toxicants. The project objective is to elucidate the mechanisms involved in injury to the airway epithelium after exposure to either an important pollutant of photochemical smog, ozone, or to a common bacterial pathogen, endotoxin. In rats repeatedly exposed to ozone, nasal airway changes include acute neutrophilic inflammation, increased epithelial cell proliferation, and secretory cell metaplasia. These changes are restricted to the transitional epithelium in the anterior nasal airway. The reason for the site-specific nature of these changes is unknown. Studies are designed to answer this question and determine the biochemical, molecular, and cellular events in the pathogenesis of this ozone-induced lesion. Previous studies have suggested that the ozone-induced epithelial changes are independent of the acute inflammatory response (i.e., neutrophil-independent). In contrast, these researchers have demonstrated that the hypersecretion of airway mucous after endotoxin instillation is neutrophil-dependent, and endotoxin is not a direct mucous secretagogue. Future studies elucidate the mechanisms of neutrophil-dependent mucous hypersecretion in airways. Repeated endotoxin exposures induce a proliferation of airway secretory cells and increased production and/or storage of intracellular mucosubstances. In contrast to the mucous hypersecretion, which was neutrophil-dependent, this airway epithelial response was induced by the toxicant and was independent of the inflammatory response. Additional studies elucidate the cellular and molecular events in the pathogenesis of this specific endotoxin-induced alteration in the airway epithelium. (RPIS 4499(B))

026. Cellular and Biochemical Mediators of Respiratory Tract Diseases

R.F. Henderson

(505) 845-1164

\$180,000

This research is determining the biochemical events that are critical in the development of late occurring pulmonary disease resulting from inhalation of airborne toxic materials. Emphasis is on the relationship between early inflammatory responses to inhaled pollutants and the continuing response that eventually leads to late occurring disease. Previous work indicates that a persistent inflammatory response leads to irreversible, adverse structural changes in the lung, characterized by fibrosis. This project is determining the factors responsible for maintaining a persistent inflammation and the biochemical products of inflammation that contribute to the long-term damage associated with inflammation. The project studies the role of phagocytic cells (neutrophils, macrophages) and their interaction with epithelial cells in the inflammatory process by (1) identifying protective factors (such as glutathione) and noxious factors (such as oxygen free radicals) released by the phagocytic cells and (2) determining the dosimetry of inhaled pollutant gases. (RPIS 4499B)

027. Radiation Dose and Injury to Critical Lung Cells from Radon

N.R. Johnson

(505) 845-9719

\$350,000

This project develops a better scientific basis for calculating the radiation dose to the respiratory tract epithelium for Rn progeny exposures that are characteristic of either home or mine atmospheres. To estimate radiation dose to the critical cells at risk for radiation-induced cancer, these cells and their locations within the respiratory airways are identified by isolating specific cell subpopulations and determining their sensitivity to radiation injury, as expressed by cytotoxicity and cell transformation. Estimates of alpha dose to the respiratory tract epithelium from inhaled Rn progeny are made by comparing the cytotoxic response of cultured normal epithelial cells to $^{239}\text{PuO}_2$ alpha particles, where the dose is known, with the cytotoxic response in cells exposed to Rn progeny in vivo where the cellular alpha radiation is not known. The alpha particle dose in vivo is estimated from the known in vitro alpha-particle dose on the basis of equivalent cytotoxicity. Home and mine environments are evaluated for their influence on dose pattern distribution throughout the respiratory tract and their potential for inducing neoplastic transformation in the critical cells and regions of the respiratory tract. The radiosensitivity and the proliferative and progenitor capacity of different populations of human respiratory tract cells are also determined. Comparison of animal and human studies identifies the cells potentially at risk, their cellular alpha-particle dose, and the likelihood of neoplastic transformation. This information may reduce the uncertainties in the current risk estimates for the general public from indoor Rn progeny exposure. (RPIS 4722)

028. Protection of Human Subjects

R.K. Jones

(505) 845-1046

\$30,000

This project provides technical assistance to the DOE Office of Energy Research, Office of Health and Environmental Research (OHER) in implementing procedures for the protection of human subjects used in research studies supported either by the DOE or by other agencies or organizations. The major objective of the OHER Working Group on Protection of Human Subjects is the development and maintenance of a resource document to guide program offices, field offices, and laboratory personnel in the implementation of Federal regulations, DOE regulations, and DOE orders relating to the protection of human subjects in research. Additional activities include review and comments on proposals, consent forms, and assurances on research projects involving human subjects submitted to OHER for approval; review of changes in Health and Human Services procedures for protection of human subjects and consideration for their inclusion in DOE regulations and orders; and participation in training sessions to familiarize contractor, field office and program office personnel with required procedures for protection of human subjects used in research. These activities will probably be required on a continual basis, at least over the near term. (RPIS 5517)

029. Molecular Mechanisms of Radiation-Induced Cancer

G. Kelly

(505) 845-7642

\$400,000

The objective of this research is to identify the critical molecular components in the pathogenesis of respiratory tract carcinogenesis induced by ionizing radiation. Carcinogenesis is a multistep process that requires sequential alterations of the genome for cells to progress from a normal phenotype to malignancy. The researchers are identifying and characterizing proto-oncogene activation and tumor-suppressor gene inactivation in radiation-induced neoplastic and preneoplastic lesions. Once identified, these genetic alterations are correlated with histologically classified proliferative lesions to determine whether specific, differential, or temporal patterns can be identified in the progression of preneoplasia to neoplasia. These objectives arise from a need to understand, at the molecular level, critical events in pulmonary carcinogenesis. Characterizing the alterations in proto-oncogenes and tumor-suppressor genes that occur as cells respond to radiation damage increases fundamental knowledge of lung tumor biology and thereby improves the basis from which risk estimation, radioprotection standards, and treatment regimens can be derived. (RPIS 4800)

030. Premalignant Events in Radiation-Induced Lung Cancer

J.F. Lechner

(505) 845-6783

\$290,000

The objective of this research is to use in vitro and in vivo systems for respiratory epithelial cell carcinogenesis (1) to identify cells at different stages of radiation-induced progression to neoplasia and (2) to characterize the cellular and molecular changes responsible. These studies use a rat tracheal epithelial cell model for experimental carcinogenesis. The responsiveness of in-vitro-derived normal, preneoplastic, and neoplastic cells and rat-lung-tumor-derived cells to growth factors is determined in serum-free culture. Information obtained is used to examine transformed cells in vitro or in preneoplastic lesions or tumors in vivo for expression of specific growth factors or growth factor receptors. Cells at different stages of progression to neoplasia are also characterized by determining the number of additional changes they need to become neoplastic using transfection with activated oncogenes. The ability of cells at different stages of progression to express an altered phenotype in vivo is determined by histological examination of denuded rat tracheas repopulated with mixtures of normal and altered cells. Finally, putative transforming genes are isolated from cDNA libraries prepared from cultures of normal and preneoplastic cells. The cDNA libraries are screened for sequences expressed in preneoplastic cells but not normal cells or vice versa. This research aims to provide critical links between in vivo and in vitro studies of respiratory carcinogenesis by identifying and characterizing critical cellular and molecular events involved in neoplastic

progression both in vivo and in vitro. This information should lead to an improved understanding of this disease and may identify new markers useful in its early detection. (RPIS 4495)

031. Mechanism of Radiation-Induced Cancer

J.F. Lechner

(505) 845-6783

\$650,000

The project studies the mechanisms of radiation-induced lung carcinogenesis. Cellular and molecular biological techniques are used to identify early preneoplastic changes in cells from beagle dogs exposed to levels of plutonium dioxide aerosols that are known, from extensive lifespan studies conducted at the Inhalation Toxicology Research Institute (ITRI), to produce a high incidence of lung cancer within a defined timeframe. Phenotypic and genetic alterations/dysfunctions at both the cellular and molecular levels are being investigated. Alterations in lymphocyte subpopulations and function are also being studied in an effort to correlate the role of the immune system in the eventual expression of neoplasia. Information gained from investigating these early preneoplastic changes contributes to knowledge of the molecular, cellular, and immune mechanisms of radiation-induced cancer and contributes to overall understanding of the biology of cancer. (RPIS 4965)

032. Lung Cancer in Uranium Miners— Gene Dysfunctions

J.F. Lechner

(505) 845-6783

\$430,000

This project identifies: (1) which gene alterations are seminal for the development of human lung cancers caused by exposure to high linear-energy-transfer (LET) radiation and (2) which alteration arises in the earliest stages of tumor development. These gene dysfunctions are being sought in lung tumors removed from uranium miners and dysplastic cells recovered in sputa and bronchial brushing samples from uranium miners before they show evidence of clinical cancer. The tumor sample analyses will provide information as to possible molecular signatures of high LET radiation-caused genetic damage. Identification of the "early gene" alterations in exfoliated dysplastic cells acquired before the appearance of clinical cancer will increase the understanding of radiation-induced molecular carcinogenesis processes specifically, contributing to the overall comprehension of the mechanisms of carcinogenesis. In addition, the data acquired through these investigations may provide the basis for definitively screening individuals considered at risk for lung cancer because of exposure to radon or other forms of high LET radiation for specific precancerous gene aberrations. Informative advice regarding working environment and lifestyle changes that could mitigate the ultimate development of clinical disease could then be provided. (RPIS 5028)

033. Dose-Response Relationships for Inhaled Radionuclides

B.A. Muggenburg

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\$1,200,000

This research objective is to predict the long-term biological effects of inhaled beta- and alpha-emitting radionuclides in humans by using studies in laboratory animals. These studies address a number of factors that may influence the relationship between dose and effects, such as total dose and dose rate, homogeneity of pulmonary dose, age at exposure, protraction of dose, and comparison of effects among species. Dose and dose rate effects in the lung are being studied using beta-emitting radionuclides. Results indicate that the risk of lung cancer per unit dose increases as the dose rate is increased, but only at relatively high lung doses. The importance of nonhomogeneity of dose in the lung is being studied with alpha-emitting radionuclides, using monodisperse particles of $^{239}\text{PuO}_2$ and $^{238}\text{PuO}_2$ that have different activity levels. Late effects seen to date are bone, lung, and liver cancers after inhalation of $^{239}\text{PuO}_2$, and lung cancer after inhalation of $^{238}\text{PuO}_2$. Nonhomogeneity of dose to the lung, "hot particles," has not increased lung cancer incidence to date in these studies. Other lifespan studies involve dogs exposed to ^{144}Ce or $^{239}\text{PuO}_2$, as immature or aged animals. Aged dogs developed radiation pneumonitis and fibrosis earlier and at smaller alpha doses than young adult and immature dogs. Dogs and rodents have also been repeatedly exposed to ^{144}Ce or $^{239}\text{PuO}_2$ aerosols to determine if the same dose-response relationships are applicable for single and repeated exposures. Studies have been conducted in rats and nonhuman primates to provide species comparison to the studies in dogs. Comparison of the results of these parallel studies are in progress and are important in extrapolating the results of animal studies to humans. (RPIS 4494)

034. Biologically Relevant Properties of Energy-Related Aerosols

H.-C. Yeh

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\$240,000

The purpose of this research is to develop information on which to base improved health risk estimates for exposure to airborne toxicants released from energy-related activities. Emphasis is on the basic aerosol characteristics and phenomena that influence the biological fate and effects of inhaled particles and vapors. This information provides a technical basis for conducting and interpreting health effects studies with airborne materials. Specifically, researchers are (1) investigating the mechanisms of aerosol formation and characterizing the resulting airborne materials, (2) studying the means by which physical and chemical characteristics of airborne materials influence the biological fate and effects of the materials when inhaled, and (3) extending the available knowledge of basic aerosol properties and behavior, essential for assessing inhalation hazards. A Millikan cell is used to study single-particle dynamics, and an aerosol chamber is used to study particle suspension, plate-out, and particle-particle interaction.

Models are developed to describe the transport and chemical conversion of materials in these aerosol systems. A new method is also developed for producing monodisperse calibration particles with fiber- and disc-like shapes. To relate basic aerosol properties, such as diffusion kinetics and aerodynamic transport to the fate of inhaled particles, the deposition of both ultrafine particles and micrometer sized particles in human nasal casts is also being studied. The results of these studies will be incorporated into an improved mathematical deposition model. The information obtained from this project is essential to other Inhalation Toxicology Research Institute and OHER biological research programs where principles are being developed for predicting the health effects of inhaled toxicants on humans. (RPIS 3972)

035. Deposition of Radon and Radon Progeny in the Respiratory Tract

H.-C. Yeh

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\$315,000

This research quantifies the amounts of inhaled radon progeny that deposit at specific sites along the airways of the human respiratory tract. The approach is to make detailed deposition measurements in human airway casts after the methods for exposing and measuring radon progeny deposition have been validated in vivo and in vitro using nonhuman primates and nonhuman primate airway casts. During the validation studies, deposition patterns are compared for test aerosols in living primates and in casts made from their respiratory airways. These studies allow comparison of in vivo deposition and deposition in casts. The information is used to determine the appropriate conditions of air flow, humidity, temperature, and electric charge necessary for making deposition measurements in human airway casts. The casts are made from lungs obtained after autopsies of adults and children of varying ages. The deposition patterns are measured for unattached radon progeny and aerosol particles of 0.005 to 0.2 μm diameter at various flow rates through the casts. These measurements are used to formulate a mathematical model for predicting inhaled particle deposition in human airways under different exposure conditions. The model is then used to compare deposition patterns for workers exposed to radon progeny in typical underground uranium mine atmospheres with those for adults and children exposed by inhaling the air inside buildings. This model provides one means for comparing the exposure-dose relationships for miners with those of the general population. The model is a necessary step to reduce the uncertainty of assessing lung cancer risks from exposures to radon and its radioactive progeny indoors. (RPIS 5022)

Lawrence Berkeley Laboratory

Berkeley, CA 94720

Applied Science Division

036. Air Pollutant Exposures in Buildings

A. Nero

J.M. Daisey

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\$275,000

The purpose of this work is to advance scientific understanding of human exposures to and health risk from indoor air pollutants. A specific focus of this work is assessment of pollutant exposures and health risks that may be associated with reductions in ventilation and other technologies intended to decrease energy use in buildings. The baseline effort includes modeling and assessment of current indoor concentrations and health effects using available information on the parameters determining indoor concentrations and epidemiological toxicological data indicating the adverse health effects of indoor pollutants. A major focus of the effort, development of a functional exposure model, will serve as the primary basis for examining major pollutant classes.

Work on combustion emissions, which previously included detailed characterization of the emissions from various indoor combustion appliances, has now focused on estimation of exposures in the context of this model. Work on radon, recently aimed at estimating the distribution of indoor concentrations, has now turned toward examining (1) the correlation between indoor concentrations and underlying physical parameters in the context of the overall exposure modeling effort and (2) combining concentration distributions with time-activity patterns and population mobility to derive overall exposure distributions. Research on organic pollutants is directed toward assembling, integrating, and assessing existing measurements of indoor concentrations of carcinogens. Indoor concentrations are modeled wherever possible to supplement this work and to further develop and validate models. Some work has begun on development of new, biologically-based methods for risk assessment. (RPIS 1866)

Cell and Molecular Biology Division

037. Long Term Biological Effects: Carcinogenic Effects of High Linear Energy Transfer Radiation

E.L. Alpen

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\$100,000

The goal is to evaluate the relationship between the linear energy transfer (LET) of radiation and its carcinogenic potential. The relative biological effectiveness (RBE) at low doses of high LET radiation is needed to estimate risk coefficients for the induction of cancer in humans.

Project researchers are evaluating low dose carcinogenesis from high LET radiation by using the murine Harderian gland as a test system. This system is useful because tumor

prevalence can be estimated at low doses in the presence of infrequent background tumor rates. Nonstopping charged particles at any given LET from less than 1 to greater than 1,000 keV/ μ m are used. The use of nonstopping ions assures that a very restricted LET range is available. New approaches are described for investigating transformation and survival of Harderian gland cells.

Researchers have already defined the Harderian gland tumorigenesis dose-response curves for heavy ions for a wide range of LETs. The initial slopes of the dose-response curve have been determined for ^{60}Co gamma rays and for a number of ions. The ratio of the ion initial slopes to that for ^{60}Co gives an estimate of RBE. The RBE reaches a maximum for ^{56}Fe ions. Relative RBE does not decrease at a very high LET as expected. A method of radiation survival assay has been developed and the survival curve for ^{60}Co gamma rays established. Preliminary data with ^{56}Fe ions show that there is little or no effect of fractionation of the irradiation.

Preliminary project results demonstrate that RBE values for high LET radiation are at least an order of magnitude higher than for other late and acute effects or for in vitro transformation. There is no reduction of this effect at very high LET. (RPIS 3663)

038. Molecular Mechanism of Cell Effect: Molecular and Cellular Effects of Ionizing Radiations

E.A. Blakely

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\$125,000

The goal of this project is to obtain a quantitative understanding of the nature and kinetics of biological responses produced at the molecular and cellular level by accelerated atomic nuclei of varying energy density. These researchers are helping to investigate the area between two DOE research efforts: (1) ongoing DOE research on the radiological physics and chemistry of heavy accelerated ions leading to initial damage to DNA in aqueous solutions and the theoretical modeling of radiation-induced mutation and transformation and (2) DOE research on the effects of heavy ions on in vivo systems. The researchers are identifying the yield of heavy-ion-induced DNA lesions that presumably originate on DNA strand breaks or DNA-DNA or DNA-protein crosslinks and then result in chromatin breaks. The researchers are examining how the chromatin break, which may be a complex lesion representing multiple strand breaks, is modified by the cell and how this type of damage affects the cell's ability to deal with additional insults. The researchers characterize chromatin damage and restitution using the premature chromosome condensation (PCC) technique to rapidly evaluate early yields of DNA damage and to follow chromatin rejoining kinetics and resulting aberration yields that are inherited by daughter clones. It has been shown that there is a linear energy transfer (LET) dependent variation in the efficiency per unit dose for the production of initial chromosome breakage, that the distribution of breaks becomes progressively overdispersed with increasing LET, and that there is a LET-dependent increase in the proportion of nonrejoining breaks. An in situ hybridization technique coupled to fluorescent

staining of PCC spreads has confirmed the linearity of the dose response for initial chromatin breakage in a single human chromosome in a human-hamster hybrid cell and has allowed an assessment of a class of misrejoining events. Recent progress has been made in showing for the first time that there is a synergistic effect on normal hamster cell survival when moderate heat is applied immediately after heavy ion irradiation, while in the absence of normal protein synthesis in a temperature-sensitive hamster mutant, the effect is merely additive. Increased new synthesis of proteins appears to interfere with cellular processing of radiation-induced damage; there are also indications of differences in the handling of high versus low LET damage. The researchers have begun an investigation to characterize protein synthesis profiles of these cells, using initially a heat shock protein (hsp 70 probe), to understand the involvement of new protein synthesis in the processing of x-ray and heavy-ion induced DNA damage. In the future, researchers will emphasize a search for specific LET-dependent, radiation-induced alterations in genetic expression. (RPIS 0305)

039. Risk Assessment in Carcinogenesis

L.S. Gold

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\$200,000

Results of more than 4,500 chronic rodent carcinogenesis bioassays on approximately 1,100 compounds are readily accessible for analysis in the researchers' (Lois Gold and Bruce Ames) Carcinogenic Potency Database. The researchers are using this vast resource to rank possible carcinogenic hazards to humans and to assess the validity of interspecies extrapolation in carcinogenesis.

The researchers have shown for 10 different data sets that about half of the chemicals tested in rodents are positive for carcinogens, including half of natural chemicals. Thus, humans are likely to be exposed to an enormous background of natural chemicals that would likely be positive in rodent bioassays at the maximum tolerated dose. Natural pesticides that are rodent carcinogens commonly occur as food constituents and usually occur at much higher concentrations than synthetic pesticides. The researchers analyzing these results emphasize the importance of ranking potential hazards. Possible carcinogenic hazards to humans from various chemical exposures are being ranked on a Human Exposure/Rodent Potency (HERP) index that expresses each human exposure (daily lifetime dose in mg/kg) as a percentage of the rodent TD50 (in mg/kg/day). HERP values will be compared for synthetic pollutants, chemicals that occur naturally as food constituents or from the cooking of food, drugs, and permitted chemical exposures for U.S. workers. In order to evaluate energy-related risks, it is important to know more about the background of natural carcinogens. For example, coffee contains about 1,000 chemicals: 22 have been tested for carcinogenicity and 17 are positive. Based on earlier ranking work, the researchers suggest that carcinogenic hazards from current levels of water pollution or pesticide residues are likely to be of minimal concern relative to the background levels of natural substances.

The validity of interspecies extrapolation from animal tests to humans will be examined by comparing results on positivity, target organ, and carcinogenic potency between nonhuman primates and rodents; between different routes of administration; and between rats and mice. Extrapolation from the high doses of rodent tests to the low doses of most human exposures will be addressed in analyses to investigate mechanisms of carcinogenesis: the associations are among mutagenicity, maximum tolerated dose, and positivity of the carcinogenic response. The researchers also hope to determine whether mutagens are more often positive at some target sites or multiple target sites than nonmutagens and whether the shape of the dose-response curve is systematically different for mutagens and nonmutagens. (RPIS 5263)

040. Biological Effects of Magnetic Fields

R.P. Liburdy

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\$250,000

Mechanisms of interaction of ultra-high intensity, ultra-high frequency, and ultra-fast switched magnetic fields with biological systems are being investigated. Exposure frequencies ranging from DC to GHz are employed, and research includes study of animal, tissue, and cellular systems. This research supports exposure guidelines for industrial, research, and medical environments. New biotechnologies based on the above magnetic field interactions have been developed, and advances have been made in drug delivery, high performance liquid chromatography (HPLC), and spectroscopy of living cells.

Studies at the cellular level indicate rat lymphocytes, when activated by mitogen to undergo signal transduction, show decreased calcium influx during 60 minute treatment in static magnetic fields of 7.5 and 9.0 Tesla, but not at 2.3 Tesla. Exposure of activated rat and human lymphocytes to nuclear magnetic resonance (NMR) imaging fields (2.3 Tesla DC; 1 Tesla/sec, dB/dt; 100 Mhz, 64 uT, RF) shows increased calcium influx; individual fields show no detectable effect. Field combinations appear to play an important role and are being investigated. Whole animal exposures to these NMR imaging fields lead to no effect on blood-brain permeability in the rat. Advanced fluorescence microscopy systems are set up to perform quantitative photometry and digital imaging of cells during exposure to electric and magnetic fields. Technology transfer is evolving in two areas. Microwave triggered drug delivery from liposome vesicles has potential for cancer therapy; pulsed-field HPLC is effective in separating large biopolymers, such as DNA, faster than pulsed-field gel electrophoresis.

Future bioeffects studies will focus on using fluorescent probes to quantitate, at the single-cell level, effects of electric and magnetic fields on lymphocyte signal transduction processes. The project is performing the first single-cell measurements of $[Ca^{+2}]$ in lymphocytes exposed to static magnetic fields up to 9.0 Tesla and to ultra-fast switched magnetic fields up to 1,000T/s. Both are being considered in advanced NMR imaging systems. In addition, biochemical markers of

lymphocyte activation such as inositol phosphate production, protein kinase C activation, and subsequent DNA synthesis are being followed. Biotechnology transfer in microwave triggered drug delivery and pulsed-field HPLC are being pursued with industry. (RPIS 2189)

041. Bone Marrow Stem Cells and Stromal Microenvironment

M. Narla

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\$60,000

This research consists of two distinct projects dealing with the biology of the hematopoietic stem cells. Long-term repopulating stem cells (LTRC) cannot be replaced after birth except by self-renewal or transplantation, yet they are the source of all blood cells throughout an animal's lifetime. Hence, LTRC must balance self-renewal (maintenance of the LTRC compartment) versus differentiation (supply of blood cells to the periphery) to fulfill both functions. The regulation of this balance is thought to be mediated by stromal cells. Project I studies functional characterization of embryonal sources of LTRC. Project II focuses on the role of stromal cells in the regulation of these primitive stem cells. Improved understanding of these key areas in stem cell biology will lead to the rational design of future bone marrow transplantation protocols that are the keystone of therapy for radiation exposure and many cancers.

In Project I, approaches are delineated using embryonal sources to obtain enriched populations of LTRC and the use of genetic constructs in transgenic animals to study their biology and function. Project II examines the role of stromal cells in regulating stem cell self-renewal versus stem cell differentiation. Delineation of the critical factors regulating LTRC maintenance in culture requires modification of the adherent cell layer by providing an extracellular matrix to the stromal cells, which allows them to express their physiological functions appropriately. The two distinct parts are closely related and provide significant new insights into stem cell biology. (RPIS 5604)

042. Rapid Transformation Assay: Induction and Detection of In Vitro Transformation of Human Mammary Epithelial Cells

M.R. Stampfer

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\$50,000

The long-term objective of this project is to develop methods for detecting carcinogen-induced transformation in vitro of human mammary epithelial cells (HMEC) such that the researchers can (1) define what characteristics distinguish normal from transformed HMEC in culture and (2) determine which agents acting alone or in combination may be capable of inducing human carcinoma. The immediate objective is to understand the relationship between the differentiated state of the mammary epithelial cell and its potential for undergoing malignant transformation.

To achieve these objectives, the researchers are utilizing the well-characterized HMEC culture system developed in the Lawrence Berkeley Laboratory. Normal HMEC, cells that proliferate rapidly both in mass culture and as colonies, are available from donors of all ages and pathologies. These HMEC rapidly metabolize benzo(a)pyrene (BaP), forming products and DNA adducts in a pattern similar to that found in cells transformable *in vitro*. BaP exposure of HMEC from one normal individual has led to the development of two immortal transformed cell lines. These lines have been malignantly transformed by exposure to tumor viruses and oncogenes.

The main problems in developing assays for transformation of HMEC lie in the general difficulty of obtaining any induced transformation of normal human cells by physical carcinogens and in defining quantifiable markers of mammary epithelial cell transformation. As a result, researchers have focused more effort on understanding the factors that might influence the capacity of HMEC to transform in culture. In particular, researchers are investigating how the differentiated state (1) changes as a result of immortal or malignant transformation, and (2) may affect the ability of the cell to undergo transformation. Specifically, researchers are extensively studying a newly isolated gene, NB-1, whose protein product bears 85 percent homology with calmodulin. This protein is expressed in normal cells from stratified and pseudostratified epithelium, but is greatly reduced or absent in transformed cells from these tissues. Researchers are exploring the possibility that the loss of expression of this protein may be correlated with the capacity of the cells to become transformed, as well as with the differentiated state of the cell. (RPIS 4296)

Lawrence Livermore National Laboratory Livermore, CA 94550

Biomedical Sciences Division

043. Human Sperm Chromatin and Chromosomes

B.F. Brandriff

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\$240,000

The objectives of this project are to (1) investigate cellular and molecular mechanisms affecting chromosome and chromatin characteristics of the mature human sperm in order to quantitate differences in organization between sperm and somatic cell nuclei and (2) validate the detection of long-lived sperm and chromosomal abnormalities as an indicator of adverse environmental effects on human spermatogenesis. A model system is being used in which human sperm are fused with eggs from the golden hamster. The eggs decondense the tightly packaged sperm chromatin and process it into interphase pronuclei and mitotic chromosomes, after which the sperm and egg die. The conformational position that sperm chromatin assumes in pronuclei offers the possibility of examining the characteristics of chromatin in a highly extended state and of quantitating differences between sperm and somatic chromatin organization and function. The examination of chromatin in the

excited state is accomplished by high resolution fluorescence *in situ* hybridization. Through this technique, cloned DNA probes for specific DNA sequences are labeled, annealed to complementary sequences present in nuclei fixed on microscope slides, and localized by fluorescent reporter molecules. From the first results, it was concluded that sperm interphase chromatin is approximately threefold less condensed than that in fibroblasts. The project is investigating the distribution of individual chromosome domains in pronuclei, characterizing the arrangement of centromere-specific DNA sequences, and quantifying differences in the degree of coiling of individual chromosomal regions. Characterization of persistent chromosomal effects following chemotherapy and radiotherapy using cytogenetic analyses of human sperm chromosomes is also being continued. These molecular and chromosomal data are combined with the earlier results on chromosomal aberration frequencies in individual human sperm cells to refine the understanding of sperm genetic attributes that contribute to normal reproduction and to the human heritable mutation load. (RPIS 4221)

044. Mechanisms of Somatic Mutation in Mammalian Cells

I.M. Jones

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\$250,000

This project combines the disciplines of mutagenesis and molecular biology to understand the mechanisms of *in vivo* induction and persistence of spontaneous and induced genetic damage. Mechanisms of DNA damage are studied using mutation as the endpoint. Interspecies comparisons employ lymphocytes as the reporters of *in vivo* induction and persistence of DNA damage to both mouse models and humans. At the molecular level, DNA damage in cells selected for deficiency of hypoxanthine phosphoribosyl transferase (HPRT) gene function is ascertained by polymerase chain reaction amplification of messenger ribonucleic acid (mRNA) and genomic DNA, sequencing of these products, and Southern analysis of mutant genes. These researchers have initiated studies of *in vivo* mutation to human lymphocytes, to parallel ongoing studies in the mouse model. The frequency of mutants detected in young adult humans is 4 times that previously detected in young adult mice. In support of this work, a new statistical approach has been developed for analysis of limiting dilution mutation assay data. Initial studies of human lymphocyte HPRT-deficient mutants detect a much higher proportion of small or point mutations than detected previously in unexposed mice. In pursuing this analysis of mutation spectrum, both for sequencing and for Southern analysis, the researchers have converted to more efficient and environmentally sound methods. Analysis of the deletion, insertion, and rearrangement mutants among the mutant human lymphocytes are being conducted in parallel with the studies of spontaneous, radiation-induced and chemically induced mutants isolated from the mouse model. These methods provide an invaluable basis for interspecies comparisons of the factors that affect the *in vivo* repair of damage to chromosomal DNA. (RPIS 4909)

045. Molecular Cytogenetics*J.D. Tucker**(510) 423-8154***\$330,000**

This project focuses on cytogenetics to understand the mechanisms of induction and persistence of spontaneous and induced genetic damage. Project goals are to (1) develop DNA probes for use as cytological markers in gene ordering, (2) validate DNA probes useful for qualifying stable cytogenetic damage using a procedure known as chromosome painting, and (3) improve automated methods of cytogenetic analysis. To accomplish these goals, synthetic "molecular-defined" chromosome bands are being developed by using yeast artificial chromosomes (YACs). YACs made of human DNA are separated from the yeast chromosomes on pulsed-field gels, digested with restriction enzymes, ligated to synthetic oligonucleotide linker-adaptor sequences, and amplified with the polymerase chain reaction (PCR). The synthetic nucleotide biotin-11-dUTP is included in the PCR solution so that the DNA probes can be detected with fluorescence in situ hybridization. Validation of chromosome painting is being accomplished using irradiated human peripheral lymphocytes in which stable chromosome aberrations (i.e., translocations) are quantified and their frequencies compared with results obtained using the more conventional method of trypsin-Giemsa banding. The analysis of Giemsa-banded material is being performed on the AKS II karyotyping machine, which has undergone further substantial refinements and is now used routinely for the analysis of stable chromosome aberrations by banding. (RPIS 3743)

Los Alamos National Laboratory**Los Alamos, NM 87545****Life Sciences Division****046. Molecular Mechanisms of Radiation-Induced Mutations***D.J. Chen**(505) 667-2789***\$150,000**

This project studies the cellular and molecular basis for gene and chromosome mutations induced by high linear energy transfer alpha particles in normal diploid human fibroblast cells. Specific aims include the following: (1) determination of the mutation-induction frequencies and the relative biological effectiveness for mutation of alpha particles with various energy (1.1-3.7 MeV) and linear energy transfer (100-200 KeV/mm), (2) molecular analysis of the type and extent of damage at or near the human hypoxanthine phosphoribosyl transferase locus, and (3) development of a Chinese hamster ovary/human hybrid line containing only a single human chromosome in the hybrid cells. This hybrid line is then used for comparative studies with the hemizygous (HRT) locus in normal human fibroblasts. (RPIS 5016)

047. Chromosome Damage in the 1 Rad Region*E.H. Goodwin**(505) 667-0072***\$210,000**

Naturally occurring levels of ^{222}Rn in the U.S. have been associated with increased risk of developing lung cancers. Accurate estimates of this risk are difficult to make, because it is nearly impossible to experimentally quantitate the deleterious effects of radiation at doses that represent the levels of radon normally encountered. Radiobiological data is desperately needed in the low dose region, not only for the sake of direct measurement, but also for the constraints such data are likely to place on models of radiation action currently used to assess low level risk. This project's objective is to directly measure breaks produced in the chromosomes of normal human cells following doses of a radiation in the 1-10 rad range by means of premature chromosome condensation. Then, by correlating cytogenetic endpoints with cell killing, a dose response is determined to alpha and gamma radiations at the limiting low dose rate for human cells. The ratio of "limiting slopes" thus obtained (alpha/gamma) is used to project the relative biological effectiveness of alpha particles from radon to situations of extremely small absorbed dose. (RPIS 5014)

048. Regulate Mammalian Cell Cycle Progression*L.R. Gurley**J.A. D'Anna**D.A. Chen**(505) 667-2726***\$250,000**

This program is determining the molecular mechanisms that regulate DNA synthesis and cell cycle progression in response to ionizing radiation. The investigations are focused on the regulation of cdc2-function kinases, which play a central role in cell cycle progression, and the molecular mechanisms that regulate inhibition of DNA synthesis at mammalian origins of DNA replication. Cells synchronized in different phases of the cell cycle are irradiated (with orderly dose progression) to determine how irradiation affects subsequent cell cycle progression, histone H1 phosphorylation, the activity of cdc2-function kinases, cdc2 kinase interactions, and DNA replication in different parts of S phase. An apparent early origin of DNA replication located near the rhodopsin gene in Chinese hamster ovary (CHO) cells is being pursued as a structural/functional model of radiation response in these studies. Recently, high-performance liquid chromatography has been used to identify the interphase and mitotic phosphopeptides of histone H1 (a major substrate of cdc2 and cdk2 kinases), and a multiprotein-binding DNA segment has been located in the early replicating rhodopsin origin region. The hyperradiosensitive CHO mutant xrs-6 will be used to determine the lowest doses of ionizing radiation that activate the indicated mechanisms of regulation. (RPIS 5639)

049. Transgenic Cell Models of Human Radiation Sensitivity

M.A. MacInnes
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\$250,000

This research is determining the cellular, biochemical, and mutagenic consequences of targeted transgenic mutations in a DNA excision repair (ER) gene. Research objectives include the following:

- (1) Development of transgenic mutations of the human Excision Repair Cross species Complementation, group 5 (ERCC5) gene that produce ER deficiency in human cells without loss of cell viability.
- (2) Development of directly comparable transgenic mutations of the mouse ERCC5 gene.
- (3) Assessment of the normal tissue-specific expression of ERCC5 gene in mouse development.
- (4) Determination of transgenic cell susceptibilities for ultraviolet (UV) and chemical-induced cytotoxicities and low-dose mutagenesis.
- (5) Determination of the extent of biochemical defects of ER at genome and gene levels in these cells.

Current progress includes isolation of both human and mouse ERCC5 genes. Cosmid and cDNA clones of human and mouse ERCC5 genes correct the UV and ER deficiencies of hamster UV135, UV-sensitive cells. Sequences of the mouse and human ERCC5 cDNAs (both 4.6 kb) are being completed for making transgenic constructs. The significance of this work includes development of directly comparable mouse and human transgenic cell models. These cells will permit elucidation of critical transgenic mutant phenotypes (e.g., cell viability, UV sensitivity) before they are introduced into mice. However, an eventual animal model will exploit ER deficiency as a controlled susceptibility factor for tissue-specific carcinogenesis. Future transgenic animal models may also be the best vehicle for developing insights about the role of DNA excision repair in growth, development, and tissue maintenance in vivo. (RPIS 5630)

050. Dosimetry and Cell Killing

M.R. Raju
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\$125,000

The objectives of this research are to (1) provide an alpha-particle exposure facility and the related dosimetry for all investigators from the Life Sciences Division and (2) conduct basic studies of the mechanisms of cell killing by alpha particles. The first objective is implemented successfully and the source is used by investigators in the Life Sciences Division. This research concentrates on studies of radiobiological effects of alpha-particle terminal tracks. This project aims to (1) provide dosimetry, (2) conduct basic studies on cell killing by alpha-particles and to probe cell nuclei using different alpha energies in an attempt to detect putative locations of sensitive targets within a variety of cell populations, and (3) investigate the cell killing, mutagenic, and transformation potential of low energy (~1 MeV) alpha particles.

The cell killing studies use five cell lines: V-79 Chinese hamster fibroblasts, flat and round shaped hamster cells CHO-10B, HS-23 with similar intrinsic radiosensitivities, 10T1/2 mouse fibroblasts, and normal human skin fibroblasts (AG1522). Although these studies concentrate on alpha-particle irradiations, control experiments with ⁶⁰Co gamma rays also are carried out where appropriate. A lack of data exists on cell killing, mutation, and transformation for low energy alpha-particles with ranges comparable to or shorter than the dimensions of mammalian cell nuclei. These studies provide some of this crucial data. (RPIS 5018)

Oak Ridge Institute for Science and Education

Oak Ridge, TN 37831

Science and Education Division**051. Technical Assistance for Committee on Interagency Radiation Research and Policy Coordination**

W.R. Boyle
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\$100,000

This task provides technical assistance for the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC), Office of Science and Technology Policy, Executive Office of the President. It includes the following:

- (1) Data research and analysis involving such disciplines as nuclear medicine; health physics; radiation biology; legal, financial, organizational, and administrative management analysis; legislative and regulatory analysis; data retrieval and library services; and outside technical expertise.
- (2) Technical assistance to the interagency staff of CIRRPC, its Policy and Science panels, and associated subpanels that provide policy and resource guidance for radiation research and policy coordination. Assistance may include recording deliberations, drafting directives and other communications, or maintaining records and library materials for the Chairperson of CIRRPC. Technical assistance also includes support of conferences, meetings, and seminars as well as assistance in the development of special publications, reports, and appropriate audiovisual and background materials. (RPIS 4584)

052. Technical Support for Implementation of the DOE Human Subject Policy

D. Minner
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\$50,000

This task (1) provides DOE with technical support for the implementation and conduct of the DOE Human Subjects Policy and (2) assists DOE in the assurance that this policy is effectively observed. The policy applies to all departmental elements, all contractors, and recipients of financial assistance performing work for the department as provided by law and/or contract and as implemented by the appropriate contracting office. Work performed at DOE-owned, -leased, or -controlled facilities, but which is not funded by DOE, is included.

DOE has a continuing concern that legal and ethical issues involved in the use of human subjects in DOE research programs be addressed fully. The need for human subjects must be addressed and justified thoroughly for proposed studies involving human subjects. DOE Order 1300 on this subject has been issued. Tasks include the following:

(1) Reviewing and revising, as appropriate, guidance needed for implementation of the DOE order and rule.

(2) Providing for orientation or education meetings and/or regional briefings as requested.

(3) Providing technical assistance on issues involving the protection of human subjects.

(4) Developing an approach for auditing and assuring quality and effectiveness of this program for prompt review of materials submitted to DOE. (RPIS 5000)

Science/Engineering Education Division

053. Alexander Hollaender Distinguished Postdoctoral Fellowships

L. McCamant

A. Wohlpart

(615) 576-1089

\$627,000

The Alexander Hollaender Distinguished Postdoctoral Fellowship Program provides a flow of exceptional scientists into DOE and university laboratories. These scientists support current and long range research needs of DOE/OHER through continued postgraduate education and training. Fellowships are tenable with OHER-sponsored investigators conducting substantial research efforts in support of OHER's mission. The goals of this mission are to (1) understand the health and environmental effects associated with energy technologies and (2) develop and sustain basic and applied research programs concerning biomedical and environmental sciences for which DOE has responsibility or unique capabilities. The research areas encompassed by this Hollaender program include the following: (1) atmospheric, marine, and terrestrial systems; (2) molecular and subcellular mechanisms underlying human somatic and genetic processes and their responses to radiation and other energy-related agents; (3) nuclear medicine; (4) structural biology; and (5) development of instrumentation necessary to achieve programmatic success. The fellowships are designed to increase the number of science and engineering graduates in specific technical areas. They support the recommendation of DOE's Energy Research Advisory Board in 1988 to "increase support through expansion of the targeted graduate and postgraduate research fellowship programs with emphasis given to energy-related areas of greatest projected human resource shortages." The program maintains approximately 180 fellowship-months (15 full time equivalencies) per year. In some years, up to 10 new fellows are selected; and 5 new fellows are selected in alternate years. Commitments to participants cover several fiscal years. (RPIS 4819)

054. OHER/Historically Black Colleges and Universities Faculty and Student Research Participation Program

D. McCleary

A. Wohlpart

(615) 576-3421

\$98,000

The OHER Historically Black Colleges and Universities (HBCUs) Faculty and Student Research Participation Program advances the mission of OHER, strengthens relevant research capabilities and academic programs at HBCUs in areas supportive of OHER, introduces HBCU faculty members and students to the OHER mission and DOE facilities, and helps to meet the requirements of Executive Order 12677. These objectives are accomplished through faculty and student research appointments at OHER research facilities for approximately 10 weeks during the summer. Participants train beside OHER scientists and become familiar with OHER-supported research. The linkage between the DOE R&D facilities and faculty members strengthens teaching and research capabilities at HBCUs, fosters collaborative interactions and technical support, and provides access to facilities and expertise not available on campus. When faculty participants return to their campuses they are able to incorporate the newly gained knowledge into the curriculum and research programs of their campuses. They are also in positions to prepare proposals that are responsive to the OHER mission. (RPIS 4403)

Oak Ridge National Laboratory

Oak Ridge, TN 37831

Biology Division

055. Mammalian Chemical Mutagenesis Program

W.M. Generoso

L.B. Russell

G.A. Sega

(615) 574-0860

\$400,000

The comprehensive long-term program in mice is designed to (1) clarify the mechanisms that guide the complex process of in vivo mutagenesis from formation of chemically induced lesions in germ cells to expression of mutations in progeny, (2) produce mutations that are useful in molecular structure/function characterization of the mouse genome, (3) understand the role of mutational processes in the etiology of mammalian and human developmental anomalies, and (4) serve as a national resource in providing state-of-the-art expertise and test systems as well as heritable mutation data for evaluating genetic risks.

To accomplish these objectives, the study (1) investigates the biological and physical factors that influence the yield of inherited mutations, including factors responsible for sex-specific mutational response; (2) investigates the role of retroviral integration in induced mutagenesis; (3) studies the nature of chemicals that pose female-specific risks; (4) develops and validates methods for measuring frequencies and/or organismic

effects of inherited lesions; and tests selected chemicals to assess genetic risks to exposed humans and/or to enlarge the germ cell database. Different classes of heritable effects are involved in these various investigations, including gene mutations, structural or numerical chromosomal aberrations, and retroviral integration. (RPIS 1570)

056. Mammalian Biochemical Genetics

R.A. Popp

(615) 574-1205

\$325,000

The purpose of this research program is to determine mutagenic and health effects of energy technologies. Mice are used as experimental animals to predict long-term effects of irradiation, chemicals, and viruses on human health. The organization and regulation of genes and the structure and function of gene products are analyzed to gain basic knowledge about the mechanics of naturally occurring and induced mutations. Physiological and pathological consequences of diseases are of special interest. Animal models of human alpha- and beta-thalassemia are inbred to develop and test alternative techniques of gene therapy that may have future applications for treatment of human thalassemia. A mouse model of sickle cell anemia is being developed using mice with mutant hemoglobin genes and human globin transgenes. In other studies, recombinant DNA, flow cytometry, and immunological methods are used to determine the mode of viral transmission and specific T- and/or B-cell lymphocytes affected in viremic mice. B10.F mice are born with a unique maternally transmitted ecotropic virus. Integration of this virus causes immune deficiency. These studies provide information on immune deficiency associated with viral integration, as well as the time of infection in the developmental maturation of T- and B-cell lymphocytes. (RPIS 0173)

057. Mammalian Genetics

L.B. Russell

W.M. Generoso

E.M. Rinchik

P.B. Selby

(615) 574-0860

\$2,100,000

This program seeks information needed for the estimation of genetic risk from radiations and other mutagens. It is increasingly devoted to indepth genetic analyses of those mutations that provide the necessary tools for molecular studies, and to the production of genetic constructs for such studies. Its emphasis is on five genomic regions for which researchers seek to relate DNA structure to function. In addition to using numerous rearrangements that have arisen in mutation-rate experiments, the program is searching for effective inducers of deletions and other specific types of genetic lesions, and for improved genetic constructs to detect such lesions. Another program underway is indepth study of the pathology exhibited by certain mutant phenotypes (e.g., immune system involvement, growth factor deficiency), including some that show promise of paralleling human disorders. Among risk-related

studies in progress are the identification of intrinsic factors affecting the nature of germ-cell mutations and the study of translocation induction under conditions paralleling prevalent human exposure. The program also produces mice for other Field Work Proposals in the Section, and maintains stocks of mutants generated in past experiments. (RPIS 0174)

058. Freezing Mouse Mutants

L.B. Russell

(615) 574-0860

\$97,000

A cryopreservation program is underway for stocks of mice that have been developed in the course of mammalian genetic studies at Oak Ridge National Laboratory (ORNL). Some of these stocks propagate mutants that have arisen over the past decades in mutagenesis tests, and that are continuing to arise in current experiments. Several of the mutants are likely to be good models for human genetic disorders and/or to have great value for molecular studies on mammalian gene structure and function. Other stocks, while not carrying induced mutations, were especially constructed for use in genetic testing or in the detection of certain mutational events. (Among these are special combinations of markers, sets of congenic stocks, and inbred strains not being carried at other laboratories.) The objective of the embryo-freezing program is to preserve some of this invaluable genetic material for further research (as the resources for such investigations become available at ORNL, or as other laboratories perceive a need for specific mutants in the future). Another objective is to free up ORNL's stock-maintenance resources for use on new mutants that are constantly being generated and must be bred. Because the laboratory strives to use optimum cryopreservation procedures, variables in technique are occasionally tested. (RPIS 3555)

059. Genetics Hazards of Radiation

P.B. Selby

(615) 574-0855

\$369,000

Although the direct method for estimating genetic risk in humans has several acknowledged advantages over the doubling-dose approach, several remaining uncertainties prevent its general use. The primary purpose of this program is to remove some of these uncertainties by determining, both qualitatively and quantitatively, the genetic damage found in first-generation descendants of mice exposed to various types of radiation. The major emphasis is placed on determining the frequency of induction of dominant mutations causing malformations that have clinical significance to humans. Of the various types of damage detected, skeletal damage has proved the most useful for estimating human genetic risk from radiation. Results of earlier specific-locus and skeletal-mutation experiments with plutonium are being prepared for publication or are under analysis. A large experiment is in progress using the assessment of dominant damage approach to identify several types of organismic damage caused by radiation-induced dominant mutations. The endpoints under study in F1 offspring include skeletal malformations, cataracts, stunted growth, other

externally visible abnormalities, and survival. Results for 600 R of low linear energy transfer ionizing radiation, delivered at either 4 mR/min or 89 R/min, are compared to each other and to the concurrent control. (RPIS 2527)

060. Mechanisms in Radiation Carcinogenesis

M. Terzaghi-Howe

(615) 574-3971

\$180,000

X irradiation alone does not induce cell populations with altered growth capacity in intact tracheas. Altered populations are observed only if proliferating monolayers or suspensions of tracheal epithelial cells (TEC) are exposed. These data suggest that in the intact tissue potentially oncogenic effects of x rays are modified. This project attempts to define those attributes of x rays that render it an "incomplete" carcinogen for TEC, relative to chemical carcinogens and high linear energy transfer (LET) radiation. Of particular interest are (1) definition of those conditions (e.g., temperature, cell contact) that affect repair of potentially neoplastic lesions and (2) evaluation of the potential of other agents (e.g., chemical carcinogens, tumor promoters, high LET radiation) to interact with x rays and to modify the lesions induced by x rays in cells in intact tissue. These experiments should provide insights into mechanisms of low LET radiation-induced carcinogenesis. A goal is to better define the influence of environment on expression of potentially oncogenic, radiation-induced alterations. Information about those characteristics rendering radiation an "incomplete" carcinogen in vivo can ultimately be used to investigate potential carcinogenic interactions between x rays, chemical carcinogens, and other "incomplete" carcinogens. (RPIS 4306)

061. The Carcinogenic Effects of Alpha-Particle Radiation on Tracheal Cells

M. Terzaghi-Howe

(615) 574-3971

\$250,000

The objectives of this research are to (1) determine the dose-response relationships of the induction of neoplastic transformation by x rays, fission neutrons, and alpha particles; (2) determine the effect of dose rate on the induction of cancer by alpha particles and fission neutrons, including the possible additive effects of alpha radiation and the effect of alpha irradiation on expression of initiation and progression; (3) determine if neoplastic transformation of rat respiratory epithelial cells exposed to radon involves specific oncogene alterations (particularly in the *ras* and *myc* oncogene families) which may exert a cooperative effect in causing expression of neoplastic phenotypes; (4) search for other genetic changes, such as possible activation by alpha-particle radiation of transposition mechanisms in endogenous mobile gene elements, which may induce cellular gene rearrangement and genomic instability in rat respiratory cells; (5) determine whether specific chromosome changes are involved in the malignant transformation of rat tracheal cells by alpha particles and other radiations; and (6) determine the relative biological effective-

ness (RBE) of alpha particles in the induction of chromosome aberrations (x rays and fission neutrons are being used as reference radiations). Data generated from the proposed combined in vivo-cell culture experiments are establishing alpha-particle dose-response relationships, in culture and in the intact tissue, for oncogenic transformation. Of particular interest is a comparison of the response (survival, oncogenic transformation) of cells exposed to similar alpha particle influences in culture and within the intact tissue. A clear resolution of these areas requires improvements, currently being made, in the protocol used to evaluate frequencies of altered cells in alpha particle-exposed populations. (RPIS 5012)

062. Mutations in Shuttle Plasmids

L.C. Waters

S. Mitra

(615) 574-0963

\$135,000

An understanding of the molecular mechanisms of mutations induced in human cells by ionizing radiation provides a basis for estimating risks to such exposures. The *supF* transfer ribonucleic acid gene, in a shuttle plasmid replicated in human cells, is used as the target for mutations involving small changes in sequence. Characterizations include mutant frequency and type and location of mutation (spectrum) as a function of radiation dose. This research group has shown spontaneous and ionizing radiation-induced mutation to be nonrandom, suggesting a specificity of base damage and/or repair, as well as an important role for neighboring bases and tertiary structure of the target DNA. The spectrum of mutations induced by alpha particles (high linear energy transfer) was very similar to that produced by x rays and to that found in unirradiated controls. There were, however, some differences between the x ray and alpha particle-induced mutational spectra, and it is postulated that these differences are due to different contributions of direct and indirect effects of radiation to the induction of potentially mutagenic lesions. Current studies are directed toward the effects of free radical scavengers on the type and distribution of point mutations and the comparison of mutational spectra induced by x rays and alpha particles in a radiation sensitive cell line, ataxia telangiectasia, and normal cells. (RPIS 5017)

Engineering Physics and Mathematics Division

063. Biostatistics and Biomathematics

E.L. Frome

R.F. Sincovec

(615) 574-6185

\$80,000

This project supports environmental research and development through research in biostatistics and collaboration with biologists, health physicists, and epidemiologists. The research (1) upgrades the statistical methodology for the evaluation of health risks in occupational cohorts and (2) designs experiments and analyzes data related to health effects of chemicals and irradiation. The research emphasizes the development of

statistical methods needed to evaluate dose-response relations in occupational studies that take into account the considerable uncertainties in dosimetry data. Statistical methodology is applied to the planning, analysis, and interpretation of biological experiments. The principal areas of collaboration support ongoing research in radiation carcinogenesis and occupation exposure to low level radiation. Work continues on the development of methods for the extrapolation of relative risk of radiogenic neoplasms across mouse strains and to man. Statistical models needed to describe the effects of dose uncertainties (both systematic biases and random measurement errors) are being developed in collaboration with dosimetry experts. (RPIS 3980)

Health and Safety Research Division

064. Radon Information Transfer

G.M. Caton

P.Y. Lu

(615) 547-7759

\$85,000

This project involves the design, development, and publication of three issues each year of *Radon Research Notes*, a newsletter that communicates activities and accomplishments of the DOE Radon Research Program, which is managed by OHER. Each issue highlights one or more of the program's research projects, other ongoing radon research, recently published literature, conference and seminar announcements, summaries of past symposia, and current events pertinent to programmatic interests. (RPIS 5096)

Pacific Northwest Laboratory

Richland, WA 99352

Life Sciences Center

065. Low-Level $^{239}\text{PuO}_2$ Lifespan Studies

A.L. Brooks

(509) 376-4487

\$250,000

This project examines temporal-spatial dose-distribution patterns for inhaled plutonium particles on Pu-induced pulmonary carcinogenesis. The emphasis is on lung tumor response at low doses and alveolar-epithelial response to aggregated Pu particles. In the study, 3,192 female Wistar, 198 male Wistar, 192 female Long-Evans, and 200 female Fischer-344 rats have been sham exposed or given single inhalation of $^{239}\text{PuO}_2$ and examined for spatial-temporal dose-distribution patterns/lung tumor formation. Histopathological analyses on 2,407 of 3,192 rats in an initial lifespan study include 793 sham-exposed controls and 1,614 exposed rats. The dose-response curve for lung tumors is well-fitted by a quadratic function with a "practical" threshold >1 Gy. ^{239}Pu appears as a promoter of pulmonary carcinogenesis at doses >1 Gy. The lung tumor threshold response with inhaled PuO_2 appears similar to threshold tumor responses in rats exposed to nongenotoxic chemicals.

Increased cell proliferation of type 2 alveolar epithelium may account for much of inhaled Pu carcinogenicity in lung. Lung tumor incidence variation between Fischer-344 and Long-Evans rats may be attributed to faster lung clearance of PuO_2 in the Long-Evans group. Brain tumor incidence in both male and female Pu-exposed Wistar rats was about twice that in control rats ($p = 0.09$); the predominant tumor type was astrocytoma. Results of this research are expected to decrease the uncertainty of tumor risk associated with low level inhaled plutonium, other alpha-emitting radionuclides, radon/ radon progeny, and high linear energy transfer radiations. (RPIS 3367)

066. Genotoxicity of Inhaled Energy Effluents

A.L. Brooks

(509) 376-4487

\$200,000

This research defines interactions between radiation-induced chromosome damage and cancer induction in three areas. First, the interaction between genotoxic damage from low dose rate exposures from internally deposited radioactive materials and subsequent or simultaneous exposure to acute external radiation is evaluated by studying the effect of linear energy transfer (LET), cell cycle stage, fraction of cells exposed, and cell type on radiation-induced changes in cellular responsiveness. Second, the role of radiation- or carcinogen-induced symmetrical chromosome exchanges in carcinogenic progression is being evaluated; these exchanges survive cell division, provide important markers of cumulative radiation dose, and are important in cell progression from normal to cancer state. Using modern molecular techniques, the researchers are evaluating the usefulness of monkey and rat respiratory epithelial cells for investigating chromosome damage and progression of respiratory tract tumors. Third, the interaction between induction and repair of gamma-ray-induced chromosome damage with that produced by chemicals, oncogenes, microbeam high LET irradiation, and random high LET radiation exposures is being studied. Understanding these mechanisms provides additional input for worker protection in the nuclear industry and during nuclear waste-site cleanup. (RPIS 5240)

067. In Vivo/In Vitro Radon-Induced Cellular Damage

A.L. Brooks

(509) 376-4487

\$225,000

Studies involving uranium miners and experimental animals can predict residential radon-progeny health hazards only if the following major radiobiological questions are addressed: (1) How do low level exposure and exposure rate affect risk? (2) What is the relationship between exposure and dose to respiratory epithelial cells? (3) How does unattached fraction influence dose distribution and damage in respiratory tract? (4) What is the biological effectiveness of radon exposure relative to low linear energy transfer (LET) radiation? Two hypotheses are being considered. First, biological effectiveness of high LET radiation for cellular and molecular damage

in respiratory epithelial cells increases with dose rate. Second, physical models of dose distribution in respiratory tract epithelial cells from radon-progeny inhalation can be validated by studying induction and repair of cellular/molecular lesions. The in vivo/in vitro approach combines animal studies with cellular/molecular experiments. Animals are exposed by inhalation to radon progeny delivered in such a way that differing dose distributions, dose rates, and total respiratory tract cell doses result. Cellular damage throughout respiratory tract cells is being measured sequentially for varying exposures. In vivo data are being related to data from exposure of rat or human cell populations. Radiological questions regarding radon-progeny inhalation risk and mechanisms of radon injury are addressed. (RPIS 5462)

068. Radon Hazards in Homes

F.T. Cross

(509) 375-2976

\$475,000

The major objectives of this project are to (1) identify and quantify in experimental animals air contaminants that produce respiratory system and other organ disease in radon-exposed populations, in mines and homes and (2) understand how these air contaminants cause cancer. Exposure-response relationships are developed in animals exposed to various combinations and levels of radon decay products (progeny) and other air contaminants. Lung cancers are produced in rats at radon-progeny exposure levels similar to those of former miners. Lung cancer incidence is influenced by the rate of exposure to radon decay products, by their attachment to dust particles, and by cigarette smoking. These studies are expected to (1) provide experimental verification of suspected cause-and-effect relationships in human epidemiology studies, (2) clarify the role of background levels of radon in causing lung cancer, and (3) provide a quantitative basis for using epidemiology data to predict health effects attributable to current low radon levels in mines and mills and in houses. Collaborative research is also directed toward understanding (1) the exposure-rate effect in radon-progeny carcinogenesis; (2) the induction-promotion relationships associated with radon and cigarette smoke; and (3) the presence, if any, of unique molecular markers associated with radon-induced cancers. (RPIS 0393)

069. Mechanisms of Radon Injury

F.T. Cross

(509) 375-2976

\$300,000

This project conducts dosimetric, molecular, cellular, and whole-animal research relevant to the toxicology of radon exposures. It focuses on exposure rate effects, induction-promotion relationships for radon and cigarette smoke exposures, the effects of radon exposure on DNA and DNA repair, and the roles of oncogenes, growth factors, and receptors in carcinogenesis. These studies contribute to a toxicologic database in animals provide an understanding of how radon exposures cause lung tumors in animals, and aid in developing predictive models for humans. A combination of molecular/

cellular, dosimetric, epidemiologic, and animal studies forms the basis for evaluating the risk of lung cancer and other health effects from human exposure to indoor radon. Radon-induced damage in vitro mammalian-cell systems and animal lungs is scaled to human exposures through knowledge of the doses received by target lung cells during inhalation exposure. Because of inherent limitations in epidemiologic data, human studies are inadequate to answer all questions concerning indoor radon. Animal data, therefore, when analyzed with models comparable to those used in human studies, provide an understanding of the mechanisms and health risks associated with indoor radon exposure. (RPIS 4721)

070. Biochemistry of Free Radical-Induced DNA Damage

A.F. Fuciarelli

(509) 376-2627

\$75,000

This project (1) investigates the influence of primary sequence and secondary structure on the types and yields of radiation-induced molecular damage to DNA, (2) compares the spectrum (types and yields) of molecular products generated in aqueous solutions of DNA exposed to high and low linear energy transfer (LET) radiations, and (3) correlates the spectrum of radiation-induced DNA products with biological inactivation using model cellular systems. Gas chromatography-mass spectrometry (GC/MS) is the most advanced technique for measuring many volatile, thermally stable DNA products. Methodologies incorporating liquid chromatography-mass spectrometry analyze those products measured by GC/MS and products that may be nonvolatile and/or thermally labile. These mass spectrometry (MS) techniques are used and refined to permit statistically reliable measurements of DNA products at low exposure doses (i.e., <10 Gy for low LET radiation). Refinements in sample handling techniques and MS methodology are applied to studies of induction and repair of molecular products in DNA extracted from irradiated eukaryotic cells. These studies provide mechanistic information on the biochemistry underlying formation and modification of molecular products generated in nucleic acids following exposure to low doses of ionizing radiation and contribute to the knowledge necessary to predict biological effects of ionizing radiation. (RPIS 5736)

071. Aerosol Technology Development

A.C. James

(509) 375-2035

\$150,000

This project's objective is to transfer aerosol and particle technology to basic and applied research in biology and health sciences. Specifically, this technology is used to develop metrology and monitoring techniques and exposure systems needed to ensure controlled and well-characterized exposures of experimental animals in studying mechanisms of carcinogenesis by radon progeny. Development of the Ultrafine Radon Progeny Size-Spectrometer (URPSS), which applies CR-39 track-etch technology to monitor alpha activity profile

deposited along a diffusion channel, will be completed with automation of CR-39 detector readout. URPSS is equally well-suited to characterize the ultrafine component of radon-progeny exposure in an animal exposure chamber, home, or workplace. This project also applies CR-39 track-etch technology to detection and analysis of activity collected by each size-selective stage of a low pressure impactor. This device serves two purposes: it (1) characterizes and records exposures of experimental animals to radon progeny attached to various carrier aerosols and (2) provides an economical and sensitive method to investigate activity-size distributions of radon progeny and other active aerosols in human domestic and occupational environments. Systems being developed expose animals uniformly to ultrafine radon progeny aerosols and radon progeny in combination with other toxic contaminants such as cigarette smoke. (RPIS 1408)

072. Microdosimetry of Radon Daughters

A.C. James

(509) 375-2035

\$110,000

This project is developing more precise methods for calculating the radiation dose to cells and cell nuclei from radon and radon daughter products. Specifically, new methods for calculating doses to both the human respiratory tract and mammalian cells irradiated in the laboratory are being developed. The biological effects of alpha-particle radiation from radon daughters begin at the cellular level. This study concentrates on the development of precise methods for calculating the variations in specific energy to sensitive cell nuclei, the mean (absorbed) dose, the probability that cell nuclei are hit or missed, and the biological consequences of discrete energy depositions in cell nuclei. The dosimetric information that results from these calculations is making it possible to evaluate the biological risks of exposure to low level environmental radon and the biological response of cells irradiated by alpha emitters under experimental conditions in the laboratory. Computational models of the microdosimetry of cells in the respiratory tract of human subjects and experimental animals and of cells irradiated in vitro by radon and daughters are being developed in this research to provide a key link to integrate information obtained from OHER Radon Program into a coherent assessment of human cancer risks from exposures to radon and thoron progeny. Given that the OHER program will succeed in defining (1) how factors such as home ventilation, air circulation, and air treatment influence the conditions of human exposure to radon daughters; (2) how carcinogenesis in experimental animals is influenced by the concentration and nature of radon progeny in inhaled air; and (3) how molecular and cellular response of cells is influenced by the concentration of radon daughters in their special environs, microdosimetric models of the effective dose to sensitive targets in each case will enable these separate strands of knowledge to be applied to assess cancer risk in the human and its dependence on exposure conditions. (RPIS 5020)

073. Inhaled Plutonium Oxide in Dogs

J.F. Park

(509) 375-3375

\$500,000

This project obtains lifespan dose-effect relationship data for inhaled PuO_2 in beagle dogs given one exposure to $^{239}\text{PuO}_2$ or $^{240}\text{PuO}_2$ aerosols, to obtain dose level groups of 20 dogs with initial lung burdens corresponding to radiation doses approximately 1, 8, 40, 150, 700, and 2,800 times the current maximum permissible lung dose for a plutonium worker. All dogs exposed to PuO_2 are now dead. Increased incidence of lung cancer has been observed in the four highest dose level groups exposed to $^{239}\text{PuO}_2$ and of lung and/or bone cancer in the five highest dose level groups exposed to $^{240}\text{PuO}_2$. Nonstochastic effects (e.g., chronic lymphopenia, sclerosing lymphadenopathy of tracheobronchial lymph nodes, liver damage) have been observed in groups that received doses equivalent to those that had increased cancer incidence. Histopathological evaluations, plutonium analysis of tissues and excreta, data analysis, and report preparation are in progress. Dose-effect relationship data obtained from this research are being used to predict the risk of these effects in humans. Tissues from these dogs are used in other projects to determine roles of oncogenes and growth factors in radiation carcinogenesis. Future research will determine the causes of lymph node damage and lymphopenia and evaluate the influence of these effects on carcinogenesis. Results of these studies will decrease the uncertainty of health risk estimates for inhaled plutonium and lead to increased understanding of the way in which high linear energy transfer alpha radiation affects health. (RPIS 1460)

074. Mutation of DNA Targets

R.P. Schneider

(509) 375-5097

\$200,000

This research tests the hypothesis that tumor suppressor genes are important targets for induction of cancer by radiation. Recent evidence in humans suggests that inactivation of the retinoblastoma (RB) gene contributes to pathogenesis of retinoblastoma, osteosarcoma, and small cell lung cancer and that p53 gene inactivation is involved in the development of most forms of lung cancer. Because deletions appear to be a major form of mutation by radiation, one would expect gene inactivation to be an important biological effect contributing to carcinogenesis. The project examines RB and p53 genes for deletions in lung cancer, osteosarcoma, and leukemia tissue from radiation-exposed dogs and rats. The analysis is performed by evaluating tumor DNA with polymerase chain reaction amplification of selected regions of the genes, northern blots, single-strand conformational polymorphism, and DNA sequencing. The research identifies altered tumor suppressor genes involved in the pathogenesis of these tumors and ascertains the site and size of the inactivating mutations. Future investigations will examine inactivation of tumor suppressor genes using transfection and cell fusion experiments with cultured cancer cells. This future research should identify tumor suppressor genes involved in these tumors and describe the nature of the mutation responsible for inactivation. The results may lead to methods that can identify markers of radiation carcinogenesis. (RPIS 4853)

075. Fetal and Juvenile Radiotoxicity*M.R. Sikov**(509) 376-3020***\$20,000**

Radiological protection standards, regulations, and procedures must adequately control exposure of pregnant workers and nonworkers, the embryo and fetus, infants, and children. Because adult radionuclide metabolism and toxicology data are not directly applicable to nonadults, these researchers have quantified radionuclide deposition, dosimetry, and toxicity in prenatal and postnatal animals. Because such quantitative values cannot be directly extrapolated to humans, mechanisms of radionuclide deposition are being determined and models for radiological protection practices for pregnant women and children are being developed. Studies of placental transfer and fetoplacental distribution of several elements relative to physicochemical and biological factors show correlation of placental transfer with fractional absorption from gut; similarities and differences are explained by binding and transport processes, metabolic specificities, and toxicities. Researchers are evaluating remaining specimens/data to complete publications on radionuclide metabolism, teratogenesis, and perinatal carcinogenesis. Mechanistic experiments on low dose effects on limb development *in vitro* determine immunocytochemical changes in extracellular matrix (fibronectin) interactions during cartilage differentiations and relationships to cell and histological changes. (RPIS 1461)

076. Molecular Events During Tumor Initiation*D.L. Springer**(509) 375-1515***\$200,000**

Even though binding of bulky adducts to DNA is known to correlate with tumor initiation, fundamental information about chromatin structure is needed. The researchers are conducting experiments on the influence of BaP-diolepoxide (BPDE) adducts on chromatin structure at the nucleosome level of organization. The pXP-14 plasmid was selected as the model system, because it forms a single nucleosome and the position of the nucleosome was known and forms at a fixed position relative to DNA sequence. Initial results using 3'-5' exonuclease activity of T4 polymerase suggested that preferred adduction sites exist on naked DNA. Studies now confirm the location of adducts to the 5S rRNA gene and SP6 promoter regions. Researchers are also determining whether adducts to DNA or core histone particles influence the formation and positioning of nucleosomes. Subsequently, the work is being extended to more complex systems, such as a plasmid containing tandem repeats of the 5S rRNA gene and the TRURAP yeast plasmid, which contains chromatin rather than naked DNA. In addition to structural changes, researchers are determining whether the adducts influence gene expression when they are transcribed by either SP6 polymerase or eukaryotic RNA polymerase III. Results provide information on the relationship among bulky adducts, chromatin structure, and gene expression and contribute to an understanding of the mechanism of chemically induced tumor initiation. (RPIS 2710)

077. Oncogenes in Radiation Carcinogenesis*G.L. Stiegler**(509) 375-1914***\$350,000**

This research examines oncogene roles in (1) induction of lung and bone tumors by internally deposited radionuclides in experimental animals and (2) leukemia in dogs exposed to whole-body irradiation. A National Institute of Health/3T3 mouse fibroblast transfection assay has detected dominant-acting "transforming" genes in tissues and cell cultures taken from malignancies. Cloned viral homologs of oncogenes, labeled by nick translation, have been used to probe DNA (Southern blot hybridization) from tumor cells and radiation-exposed nontumorous cells from the same animal. Novel (tumor-specific) restriction fragments have frequently been detected in *ras* genes from plutonium-induced tumors, indicating rearrangement of oncogene sequences in cells from radiation-induced tumors. This study is examining oncogene expression in radiation-induced cancer cells at level of messenger ribonucleic acid (mRNA) transcription (Northern Blot) and by mRNA-directed polymerase chain reaction (PCR) amplification. The project is determining frequency and distribution of *ras* mutations in genomic DNA or transcribed mRNA isolated from radiation-induced malignancies; *ras* gene sequences are amplified from tumor DNA and mRNA by PCR. Amplified sequences are molecularly cloned and analyzed by dideoxy DNA sequence analysis (Sanger Method). (RPIS 4528)

078. National Radiobiology Archives*C. Watson**(509) 375-3483***\$450,000**

The National Radiobiology Archives project is a comprehensive effort to gather, organize, and catalog data, documents, and tissues related to radiobiology studies conducted by DOE-sponsored laboratories. These Archives provide future researchers with information for statistical analysis to compare results of these and other studies and with tissues for analysis by advanced molecular biology techniques. The project concentrates initially on three tasks associated with studies of beagle dogs exposed to ionizing radiation at five DOE laboratories: (1) implementing an interlaboratory computerized information system containing a summarized dose-and-effects database, with results for each of more than 5,000 lifespan-observation dogs, an inventory database, and a bibliographic database; (2) establishing a document archives of research materials such as logbooks, clinical notes, radiographic films, and pathologists' observations; and (3) establishing specimen archives for tissue samples and histopathology blocks and slides. The databases are populated with records from the five laboratories. Tissue specimens and histopathology blocks are received from the University of California at Davis, and their document collection is being accessioned. Future tasks for this project include similar activities for selected radiobiology studies in other species. (RPIS 4529)

Radiation and Chemical Effects: Biological Effects Studies

Offsite Grants

Brandeis University
Waltham, MA 02254

Rosenstiel Basic Medical Sciences Research Center

079. Mechanisms of Repair of Double-Strand Chromosomal Breaks

J.E. Haber

(617) 736-2462

\$182,000

Low doses of radiation are important sources of DNA damage that have been implicated in the origins of many types of human cancer. This research focuses on the DNA repair mechanisms that can give rise to chromosomal rearrangements. Translocations have been implicated in the activation of oncogenes by placing them under the inappropriate control of other regulatory sequences, while deletions and somatic crossings-over have both been shown to be involved in uncovering recessive oncogenic mutations. Very little is known about the mechanisms of DNA repair that give rise to these types of outcomes. Little is known about how DNA molecules are repaired or what role(s) various gene products play in this repair process. This project seeks to understand the ways in which the normal repair of a damaged DNA differs from events that give rise to chromosomal rearrangements.

A model system is being developed using the yeast *Saccharomyces cerevisiae*, which can be used to examine the mechanisms of repair of double-strand breaks (DSB). The induction of an endogenous site-specific endonuclease creates a single double-strand break in the majority of cells in a population so that their synchronized repair by recombination can be followed at the DNA level. This system provides an opportunity to identify the series of molecular events in DNA repair and to learn the specific molecular roles of a large number of genes that have been identified by radiation-sensitive mutations.

The project examines the molecular mechanisms underlying three novel types of repair of double-strand breaks in chromosomes, in addition to the well studied gap-filling or gene conversion mechanism of DSB repair: (1) deletions caused by single-strand annealing between dispersed, homologous sequences, (2) terminal chromosomal deletions caused by de novo formation of new telomeres, and (3) deletions caused by nonhomologous ligation of degraded DNA.

Further, the project delineates the roles of specific gene functions by physically monitoring the formation of a sequence of DNA intermediates of recombination in yeast RAD mutants. (RPIS 10545)

University of California, Davis
Davis, CA 95616

Institute for Toxicology and Environmental Health

080. Skeletal Remodeling Dynamics: New Approaches with Imaging Instrumentation

N.J. Parks

(916) 752-1347

\$100,000

The intensive investigation over the last 30 years of how, when, and where various bone-seeking radionuclides, particularly alkaline earths and actinides, produce various different anatomical and temporal distributions of bone cancer and other cellular dyscrasia has revealed gaps in the fundamental knowledge of cellular dynamics in normal bone, and almost nothing about what is normal at late times in the lifespan. Using the beagle, this research experimentally tracks the activity of cells in compact bone by microradiography and fluorescent label monitoring of remodeling and mineralization. Neutron activation analysis (NAA) and dissection are being performed with selected bones from young adults through age 18 years to determine how skeletal distribution and density of cancellous and compact bone change with age. A theoretical effort to mathematically model the two-dimensional cell flux in individual osteons of young dogs is being completed, and the modeling of changes with age is compared to data from dogs fluorescently labeled at ages up to 18 years so that direct assessment of remodeling with time is possible. The three-dimensional modeling of anastomosing osteon structures, the heretofore poorly characterized changes in collagen fibril orientation in filling osteons, and the density of osteocyte lacunae are examined in young and old animals. The research looks for indications that radiation-induced uncoupling of osteoclastic and osteoblastic action may model aspects of spontaneously occurring osteoporosis. The Partitioned Clearance Model for radionuclide clearance in individual bones of beagles includes the bone surface and mass assumptions of the ICRP-20 model for alkaline earth metabolism in humans. The direct testing of metabolic (i.e., chemical) theory estimates of cortical and cancellous bone mass and available reactive surface for bone-seeking agents is made against the results of measurements with NAA and computerized axial tomography methods for mass distribution. The combination of the morphological and metabolic models is applied to translating the results of bone-seeking radionuclide studies in beagles to age-dependent risk estimates for human patients undergoing therapeutic procedures with bone-seeking radioactive agents. (RPIS 10173)

Laboratory for Energy-Related Health Research

081. Comparative Toxicity of Strontium-90 and Radium-226 in Beagle Dogs

O.G. Raabe

(916) 752-7754

\$163,000

This is a 30-year study of the biological effects of Strontium-90 (^{90}Sr) and Radium-226 (^{226}Ra) in the beagle to predict the possible long-term hazards to people from chronic exposure to low levels of irradiation. Animals received either radionuclide by several means of administration: continual ingestion of ^{90}Sr , a single intravenous injection of ^{90}Sr , or a series of eight intravenous injections of ^{226}Ra . Although administration of ^{90}Sr and ^{226}Ra ended at 540 days of age, the animals continued to receive chronic, low level radiation doses from these bone-seeking radionuclides throughout life. This project is the largest single cohort study in beagles of internally deposited radionuclides. It is unique in use of the ingestion route for ^{90}Sr and in exposures that began before birth and continued throughout development into adulthood with uniform labeling of the skeletons with ^{90}Sr . The last of the dogs died in 1986 at 18.5 year olds, but the project continues to investigate the significance of these long-term exposures given at low dose rates with regard to cancer production, physiologic well-being, and shortening of life through the detailed records that were kept and by study of preserved materials. All the data have been successfully accumulated and entered into a mainframe computer database management system. Current work is exclusively directed at preparing research papers summarizing the results and the associated biostatistical and survival analyses. (RPIS 9229)

University of California, Los Angeles Laboratory of Biomedical and Environmental Sciences

Los Angeles, CA 90024

Division of Biomolecular and Cellular Sciences

082. Developmental Neurotoxicology

J. de Vellis

(213) 825-9395

\$170,000

The main objectives of this project are to identify and characterize the endogenous and environmental agents that influence critical events in the development of the central nervous system. Cell culture and animal model systems, capable of recapitulating important central nervous system developmental events, are used to study cell lineages and to elucidate molecular mechanisms of gene expression, growth regulation, cellular differentiation, cell survival, neurotoxicity, and neoplastic transformation. (RPIS 9762(A))

083. Chemical Carcinogenesis

O. Hankinson

(213) 825-9431

\$192,000

Polycyclic aromatic hydrocarbons (PAHs) and chlorinated hydrocarbons (CHs) are major environmental pollutants and are highly carcinogenic. Carcinogenesis by PAHs depends upon their metabolism by cytochrome P-450IA1. A gene that regulates the transcription of the cytochrome P-450IA1 gene has been cloned and three others are being cloned. Three of these genes also mediate pathogenesis by CHs. The cloned genes will be used to investigate whether differences in structure or expression of any of these genes determine differential susceptibility to PAH- and CH-induced cancer in humans. (RPIS 9762(B))

University of California, San Diego La Jolla, CA 92093

Department of Biology and the Cancer Center

084. Comparative Studies in Mouse and Man

M. Haas

(619) 534-4902

\$230,000

This research aims to identify and clone the lymphoma-derived growth factor (LGF) that is synthesized by cell lines derived from radiation-induced T-lymphomas of C57B1/6 mice. This growth factor functions via an autocrine-like mechanism in the tumor cells and thus plays an important role in establishing the transformed state in these cells. The research includes purifying the LGF from supernatants, sequencing the purified protein, preparing a synthetic peptide from which monoclonal or polyclonal antibodies can be derived to recognize the protein. Alternatively, the amino acid sequencing is to be used to develop oligonucleotides that can recognize the LGF sequence in a cDNA library. (RPIS 10476)

University of California, San Diego School of Medicine

La Jolla, CA 92093

Department of Radiology

085. Yields of Biologically Significant Damage Produced in Mammalian DNA by Irradiation Associated with Radon Decay

J.F. Ward

(619) 534-4916

\$150,000

The goal of this project is to determine the difference(s) between the damage produced in DNA by alpha particles and low linear energy transfer (LET) radiation. Cellular DNA is generally accepted as the molecular target for radiation-induced cell death, mutagenesis, and transformation. The range of damage types, predicted from model systems, consists of single- and double-strand

breaks, base damage, and DNA/protein cross links. Previous studies of irradiated DNA have concentrated almost exclusively on single- and double-strand breaks. Radiation-induced alterations in DNA can be classified into singly damaged sites and locally multiple damaged sites (LMDS). Research has recently shown the former to be inconsequential biologically. The biologically significant lesion(s) can therefore be identified as LMDS. These can be formed with a variety of structures of which only the DNA double-strand break has been studied, although LMDS involving base damage is likely to be formed in much higher yield. Reasoning that LMDS is more likely to occur with the increased energy deposition pattern of α -particles than with sparsely ionizing low LET gamma radiation, this study postulates these lesions to be responsible for the increased biological effectiveness of alpha particles. Therefore, both the yields and the quality of the DNA damage(s) produced by α and γ radiation are being compared. This work shows that α -particle damage to the cellular target molecule DNA is quantitatively similar to that caused by low LET radiation. Future work is aimed at defining the qualitative difference. The relative biological effectiveness of a radiation type must be defined by this qualitative difference. Intercomparisons of qualities of damage types should permit prediction of biological effectiveness. Mechanistic considerations indicate that alpha particles may have a signature in deleting fragments about 80 base pairs long from the macro-molecular DNA. (RPIS 9813)

Case Western Reserve University Cleveland, OH 44106

Department of Radiology

086. Mutagenicity of Radon and Radon Daughters

H.H. Evans

(216) 844-3530

\$220,000

The objective of this research is to investigate the dose-response relationship with regard to the lethal and mutagenic effects of exposure of cells to radon and its decay products. Dose-rate dependence is being studied as well as the nature of the DNA lesions. The effect of DNA repair on the lethal and mutagenic effects of exposure and on the character of the DNA lesions will be investigated by comparing the response of LS178Y strains, which differ in their ability to rejoin x radiation-induced DNA double-strand breaks. The uncertainty of lung cancer risk estimates for humans from exposure to radon arises from the need to extrapolate from data obtained in epidemiologic studies (entailing high levels of exposure) to the low levels present in the majority of homes. The shape of the dose-response curves at low levels can best be determined experimentally using in vitro systems. Experiments with cell cultures such as described previously provide measurements of the lethality and mutagenesis due to low levels of radon as well as information as to the mechanism of lung cancer induction by this agent. Mechanistic studies reveal the type of lesion responsible for carcinogenic effects and the mechanism of induction of these lesions and therefore predict the dose-response relationship at all levels of exposure. (RPIS 9812)

Columbia University College of Physicians and Surgeons

New York, NY 10032

Department of Ophthalmology

087. Low Dose Neutron Late Effects: Cataractogenesis

B.V. Worgul

(212) 305-6748

\$250,000

This work seeks to resolve the uncertainty regarding the relative biological effectiveness of low dose neutron radiation. The study exploits the fact that cataractogenesis is sensitive to the inverse dose rate effect as has been observed with heavy ions and was an endpoint considered in the followup of the A-bomb survivors. The neutron radiations are initiated at the Radiological Research Accelerator facility of the Nevis Laboratory of Columbia University. Four-week-old (± 1 day) rats are divided into eight dose groups each receiving single or fractionated total doses of 0.2, 1.0, 5.0 and 25.0 cGy of mono-energetic 435 KeV neutrons. Special restraining jigs ensured that the eye, at the midpoint of the lens, received the appropriate energy and dose with relative error of $\pm 5\%$. The fractionation regimen consists of four exposures, each administered at 3 hour (± 1 minute) intervals. The neutron irradiated groups are compared to rats irradiated with 250 kVp x-rays in doses ranging from 0.5 to 7 Gy. The animals are examined on a biweekly basis utilizing conventional slit-lamp biomicroscopy and the Scheimpflug Slit Lamp Imaging System. The followups, entering their second year, continue throughout the lifespan of the animals. This is essential inasmuch as the extremely low doses being utilized are not anticipated to cause clinically detectable opacities until a significant fraction of the lifespan has lapsed. Current data supports this contention. At this juncture cataracts in the irradiated groups are beginning to exceed control levels. While extremely preliminary, the earliest data suggest that dose protraction has a modulating effect on the neutron exposure. In the case of the x ray in animals, significant sparing is observed with fractionation. (RPIS 10302)

Duke University Medical Center

Durham, NC 27710

Department of Medicine

088. Determination of the Cell Distribution and Mucous Thickness in the Airways of the Lung for Modeling Injury Caused by Inhaled Radon and Radon Daughters

R.R. Mercer

(919) 684-2513

\$130,000

To assess the effects of radon and radon progeny on the lungs, the target regions for the inhaled pollutant and the sensitivity of specific cells located in the target regions must be determined. Mathematical modeling, coupled with quantitative

anatomic data, permits determination of these critical injury sites for inhaled pollutants. This study's objective is to provide detailed data for carrying out such assessment of the effects of radon and radon progeny in the lungs. Determination of the target regions is being done by quantitative morphometric study of the distribution of the various cell types and mucous lining layers in the lungs. Current models for risk assessment are based on crude estimates of fluid layer thickness and do not distinguish between different cell types. Results of these studies will significantly improve the ability to do risk assessment for radon exposures by providing quantitative data for specific cell types along the airways. (RPIS 9816)

Fred Hutchinson Cancer Research Center
Seattle, WA 98104

Division of Public Health Science

**089. Initiation-Promotion-Initiation Experiments
with Radon and Cigarette Smoke: Lung Tumors
in Rats**

S.H. Moolgavkar
(206) 467-4868

\$112,000

Research objectives are to (1) analyze the large experimental data sets that a researcher has accumulated on lung tumors in rats exposed to radon, by using modern survival data methods and the two-mutation model of carcinogenesis, which is a generalization of the recessive oncogenesis model; (2) estimate the parameters of the two-mutation carcinogenesis model, to generate testable biological hypotheses regarding radon-induced lung carcinogenesis, and to study dose response of lung tumors in terms of the effects of radon daughters on the model's parameters (i.e., in terms of the effect of radon daughters on mutation rates and cell proliferation kinetics); and (3) help a researcher at Battelle Pacific Northwest Laboratory design Initiation-Promotion-Initiation experiments with rats showing radon daughters as the initiator and cigarette smoke as the promoter and to analyze the resulting data. The results of the analyses provide a biologically based dose-response function for risk assessment and extrapolation. (RPIS 9825)

**The Johns Hopkins University School of
Hygiene and Public Health**
Baltimore, MD 21205

Division of Environmental Health Engineering

**090. Regional Aerosol Deposition in Human Upper
Airways**

D.L. Swift
(301) 955-3602

\$105,000

The objective of this research is to elucidate important factors that influence overall and local deposition of aerosols in the human airways above the trachea, i.e., the nasal passage, oral passage, pharynx, and larynx. This is important information

for the development of dosimetric models for radon daughter and other environmentally significant airborne particles. Of particular interest are the effects of flow rate, particle diameter, and airway dimension, especially as affected by age and respiratory condition. The limited existing experimental data are only for normal adult males. Particularly lacking is the role of the upper airways of children and infants in the removal of radon progeny aerosols breathed by nose only or oronasally (mouth and nose). These researchers hypothesize that the upper airways of nonadults are not scaled versions of adult airways and thus must be treated separately when modeling respiratory tract deposition. (RPIS 9819)

University of Michigan
Ann Arbor, MI 48109

Department of Human Genetics

091. Studies of Human Mutation Rates

J.V. Neel
(313) 763-9312

\$312,000

This program focuses on developing technologies for the recovery of proteins from two-dimensional polyacrylamide gels, for sequencing and identifying their corresponding genomic DNA. Particular attention is directed to proteins characterized by variants and to nucleoproteins (and suitable controls). These genes are used for genomic mapping and mutation studies. An estimated 6-12 full-length genes (suitable for at least 100 probes for the study of mutation) should be characterized. The program is interdigitating with the attempt at the Radiation Effects Research Foundation to move the study of mutation in the children of atomic bomb survivors to the DNA level. This interdigitation extends from the role of Ann Arbor in developing probes for the study in Japan (and serving as a conduit to Japan of probes developed in this country) to R&D on two-dimensional DNA gels and the improved recovery of variant DNAs from such gels. This interaction involves the exchange of personnel between Ann Arbor and the Radiation Effects Research Foundation. (RPIS 9659)

Department of Radiation Oncology

**092. Role of X-Ray-Induced Transcripts in Adaptive
Survival Responses Following X Rays**

B.A. Boothman
(313) 764-3330

\$162,000

This research isolates, identifies, and characterizes new messenger ribonucleic acid (mRNA) transcripts induced by low doses of ionizing radiation. Their respective gene products may play a role(s) in DNA repair responses which lead to adaptive survival responses in human cells due to prior exposures of low doses of ionizing radiation. Subtractive and/or differential cDNA cloning hybridization techniques are utilized to isolate induced mRNA transcripts stimulated by

exposing human melanoma cells to low doses of ionizing radiation. Isolated genes are partially sequenced and their identities, if previously cloned, are ascertained via GenBank analyses. Previously isolated x-ray-induced cDNA clones (xip 1 to xip 12) are also investigated to see if they are induced by low x-ray doses. Antisense constructs are prepared to examine the effect(s) of specific xip gene down regulation on DNA repair, break repair, and adaptive survival enhancement responses. In addition, complementation studies using plasmid transfections into various cancer-prone cells are performed to investigate the role of each xip clone in DNA repair. This research provides a fundamental research base to elucidate the adaptive survival responses occurring in human cells following low doses of ionizing radiation. (RPIS 10603)

University of New Mexico School of Medicine

Albuquerque, NM 87131

Department of Medicine

093. Lung Cancer Epidemiology in New Mexico Uranium Miners

J.M. Samet

(505) 277-5541

\$89,000

This investigation assesses the health effects of radon daughter exposures in New Mexico uranium miners. Cumulative exposures sustained by most New Mexico miners are well below those received earlier in the Colorado Plateau. This project utilizes the research opportunity offered by New Mexico miners to address unresolved issues related to radon daughter exposure: (1) the lung cancer risk of lower levels of exposure, (2) interaction between radon daughter exposure and cigarette smoking in the causation of lung cancer, (3) the relationship between lung cancer cell type and radon daughter exposure, and (4) possible effects of radon daughter exposure other than lung cancer.

A cohort study of 3,800 men with at least 1 year of underground uranium mining experience in New Mexico is in progress. The investigation began in 1977 and since 1983 has been funded by a contract from DOE. Large databases have been assembled that describe the exposures of the miners to radon daughters and their smoking and mining histories. Mortality in the cohort is assessed periodically. To date, a four-fold excess of lung cancer has been observed. A case-control study of incident cases of lung cancer has been completed and the findings reported. The estimated excess relative risk was 1.1 percent per working level month (WLM). The data were consistent with a multiplicative interaction between cigarette smoking and exposure to radon decay products. Analysis of the full cohort data is now in progress using multivariate approaches. A panel of pathologists reviews the histopathology of all lung cancer cases.

This program is completing the multivariate analyses, continuing followup of the cohort, and implementing a case-

control study within the cohort for all cases and a matched control group of miners deceased from other causes. The case-control study provides a lifetime history of cigarette consumption and permits more careful assessment of the interaction between smoking and radon decay products. Continued followup of the cohort is needed to describe the temporal evolution of the lung cancer risk associated with exposure to radon decay products. (RPIS 10200)

094. Lung Cancer in Uranium Miners—A Tissue Resource

J.M. Samet

(505) 277-5541

\$100,000

Radon-exposed underground uranium miners in Arizona, Colorado, New Mexico, and Utah are at documented high risk for lung cancer. This project has two activities directed at obtaining biological materials from uranium miners for characterizing molecular and cellular changes during respiratory carcinogenesis: (1) continued collection of lung cancer tissue in Albuquerque, NM, and Grand Junction, CO, and (2) a pilot study to assess the feasibility of prospectively collecting biological specimens from former uranium miners. The biological specimens include blood, induced sputum, and bronchoscopically obtained washings, brushings, and biopsies from the lung. An interview obtains complete smoking information, a comprehensive history of mining and other occupations, and information on diet and other factors that may also influence lung cancer risk. If the results indicate feasibility, the pilot study will serve as the basis for designing a larger-scale project directed at the evolution of cellular and molecular changes during respiratory carcinogenesis.

The goal of this project is to develop a complementary resource to the ongoing collection of lung cancer cases in Albuquerque and Grand Junction. The materials acquired prospectively in subjects at high risk for lung cancer will be used to describe the evolution of cellular and molecular changes during respiratory carcinogenesis. Collection of lung cancer tissue from hospitals in Albuquerque and in Grand Junction and from subjects involved in the longitudinal study would provide case material. If the pilot work establishes feasibility, the proposed longitudinal collection of materials and subsequent laboratory analysis could describe the sequence of changes leading from a normal to a malignant cell and identify biomarkers of these changes. (RPIS 10789)

New York University Medical Center

New York, NY 10016

Department of Cell Biology

095. Cellular Morphometry of the Bronchi of Human and Dog Lungs

E.S. Robbins

(212) 340-5338

\$100,000

The research objective of this project is to quantify the cells at risk for radon-induced cancer in the lining (epithelium) of the large air passageways (bronchi) of the human lung. These airways are the most common sites of lung cancer. Therefore, in order to make accurate models to assess the cancer risks, the details of the distances of the nuclei of the different cell types to the lumen (space inside the airway where the radon is) must be measured. In addition, because it is presumed that radon damages DNA, the percent of the lining of the bronchial epithelium occupied by the cellular nuclei (containing the DNA) is being determined. Also, because cigarette smoking increases the risk of cancer in those exposed to high levels of radon, the bronchi of smokers and nonsmokers are being compared. Finally, male and female risks of cancer and lung parameters are not identical; the airways of men and women are being analyzed separately. With the resulting numbers, it will be possible to reduce uncertainties in selected parameters of risk models for radon-induced carcinogenesis. (RPIS 9817)

Institute of Environmental Medicine

096. Particle Deposition in Human and Canine Tracheobronchial Casts

B.S. Cohen

(914) 351-5277

\$130,000

The objective of this work is to measure deposition patterns and efficiencies of aerosol particles using a range of sizes within realistic, single-pathway physical models of the tracheobronchial airways of humans and experimental animals for a variety of respiratory modes and rates. This will provide data needed to assess the effect of particle size, breathing pattern, and respiratory tract morphology on the dose to the critical cells of the bronchial epithelium. The measurements will permit the development and critical evaluation of quantitative predictive models for the deposition efficiency of the inhaled radioactive particles. The radiation dose to the sensitive cells of the bronchial epithelium will depend critically on the efficiency with which the particles are deposited on the airway surface. In addition, the pattern of deposition is important because substantial radioactive decay of the short-lived radon daughters will take place before the initial particle deposit can be removed by normal clearance mechanisms. Few detailed data are available on particle deposition on airway surfaces in humans or animals. Important distinctions result from size, anatomy, and, especially, branching pattern. This work will provide critical

particle deposition data that will help (1) predict radiation dose from exposure to indoor radon and (2) extrapolate the results of animal studies to humans. (RPIS 9699)

097. Measurement and Apportionment of Radon Source Terms for Modeling Indoor Environments

N.H. Harley

(212) 263-5287

\$90,000

This research quantifies mechanisms for radon entry into homes of different types and determines the fraction of indoor radon attributable to each source, and models and calculates the dose (and therefore alpha-particle fluence) to cells in the human and animal tracheobronchial tree that is pertinent to induction of bronchogenic carcinoma from inhaled radon daughters. The dosimetry extends to organs other than the lung. (RPIS 10644)

Oakland University

Rochester, MI 48309

Chemistry Department

098. Mechanisms for Radiation Damage in DNA

M.D. Sevilla

(313) 370-2328

\$51,000

This project is examining several mechanisms for radiation damage to and protection of DNA and its constituents. It is also pursuing a series of experiments utilizing electron spin resonance spectroscopy to test the proposed mechanisms. In previous efforts these researchers have investigated radioprotection of thiols in the direct radiolysis of DNA. For the first time, primary radicals formed in DNA were found to react with thiols to form thiyl radicals, which subsequently react with oxygen. More current research has determined the relative abundances of primary ion radicals in x-irradiated DNA and found the following abundances: (1) 80 percent cystosine anion, (2) 20 percent thymine anion, (3) 95-100 percent guanine cation, and (4) 0-5 percent adenine cation. The fact that both cytosine and thymine anions are found is an important outcome that is believed to be a result of the stabilization of the cytosine anion by a proton shift from its guanine base pair. The transfer of charge between cytosine and thymine on annealing is now being investigated. (RPIS 9548)

Sloan Kettering Memorial Cancer Center New York, NY 10021

Medical Physics Department

099. Activation of Oncogenes by Radon Progeny and X Rays

C.C. Ling

(212) 639-8301

\$160,000

The goal of this research is to study the carcinogenic effect of radon progeny at the molecular level, utilizing techniques developed in molecular biology, cancer cell biology, and radiation biology. The underlying assumption is that malignant transformation of normal cells is a multistep process that requires activation of two or more oncogenes. The hypothesis is that radiation has the ability to activate certain proto-oncogenes and can be involved in one or more of these steps. In vitro models of transformation are being used to reproduce the stepwise progression of normal cells toward the transformed phenotype. The project examines whether radiation can provide the necessary activating function at discrete steps along this path. The strategy applied involves introducing into normal primary cells a variety of cloned oncogenes known to supply only some of the functions necessary for full transformation. These "partially transformed" cells are the targets of various forms of radiation that are assessed for their ability to (1) activate oncogenic functions that "complement" the one already present in the irradiated cells and (2) produce the fully transformed phenotype. In this way, researchers hope to identify the stages of transformation and functions important for transformation induced by different types of radiation. These studies provide the starting point for an analysis of the genetic basis of radon-induced oncogenesis. (RPIS 10124)

University of Southern California Los Angeles, CA 90089

Molecular Biology Section

100. Direct Detection of Mutations in Human Mitochondrial and Nuclear DNA Using the Polymerase Chain Reaction

G.A. Cortopassi

(213) 740-5562

\$93,000

Exposure to ionizing radiation is known to cause deleterious effects in humans, many of which are thought to be mediated by the induction of somatic and germline mutation. A new type of assay to directly determine levels of mutation from human DNA samples has recently been developed. The assay uses the polymerase chain reaction (PCR), an enzymatic technique for amplifying genetic sequences from complex genomes. The assay detects deletions of mitochondrial DNA (mtDNA) directly from purified cellular or tissue DNA. Basal (spontaneous) levels of a particular deletion mutation ($\Delta 1$) were detected in normal adult human somatic tissues with this assay and appear

to increase with age. The identical deletion occurs at high level in some rare, sporadically inherited human genetic diseases.

A PCR-based assay has several intrinsic advantages over other existing assays of human somatic mutation. The number of mutant molecules is determined directly from purified DNA; therefore, the level of somatic mutation can be determined from any source from which DNA is available, including fresh, frozen, or formalin-fixed human mitotic or postmitotic tissues. Because the assay is DNA-based, no expression time subsequent to occurrence of the mutation is required for detection.

The mitochondrial genomes' high copy number and deficiency in recombination and repair of mtDNA deletions might make this system an optimal genetic marker of radiation exposure, because the effective target size is relatively large, and multiple hits in mitochondrial targets are known not to be lethal to the cell.

This project is developing a PCR-based assay of a nuclear gene (ADA) that is thought to contain a deletion hotspot and determining the effect of ionizing radiation on absolute levels of mtDNA and ADA deletions in human tissue culture and human tissues and its effect on relative frequencies of particular mtDNA deletions (the mutation spectrum) in tissue culture. Preliminary data that affect on several of these objectives have been collected.

Experiments involve exposure of cells to the desired radiation dose, preparation of DNA from the exposed cells, and quantitative determination of the number of deleted forms relative to normal mtDNA or ADA genes using techniques already developed. (RPIS 10566)

SRI International Menlo Park, CA 94025

Cellular Genetics Program

101. Analysis of Gene-Specific DNA Adduction by Energy-Related Chemicals

C. Rudd

(415) 859-6462

\$263,000

Key molecular events induced by genotoxic, carcinogenic chemicals are hypothesized to include the interaction of the chemicals with proto-oncogenes and/or suppressor genes and the consequential induction of mutations or chromosome rearrangements at these sites. This project examines the ability of energy-related chemicals to covalently bind to specific DNA sequences in vivo and in vitro and correlates relationships between adduct formation, rates of repair, and induction of mutations. Molecular techniques are being developed to isolate specific genes from genomic DNA using biotin-labeled complementary sequences as capture probes and recA-mediated hybridization. An ultrasensitive method for quantitation of ^{14}C -labeled adducts, accelerator mass spectroscopy, has been developed at Lawrence Livermore National Laboratory; this technology is used to evaluate the relative adduction of radiolabeled chemicals in specific regions of DNA from cells exposed to the

chemical in vitro and in vivo. The usefulness of this technology for comparing adduction, repair, and mutation is examined using cells and tissues from a transgenic mouse that contains multiple copies of a selectable gene.

This research improves the understanding of the health consequences of energy-related chemicals. Technology developed as part of this project elucidates mechanisms of DNA damage and repair within various domains of the human genome. (RPIS 10569)

St. Mary's Hospital and Medical Center
Grand Junction, Colorado 81502

Department of Cytopathology

102. Early Lung Cancer Detection in Uranium Miners with Abnormal Sputum Cytology

G. Saccomanno
(303) 244-2063

\$43,000

Because most uranium miners are cigarette smokers and have been exposed to radon, the incidence of lung cancer in this population is very high. The objective of this research is to examine cells from the sputum of uranium miners in order to identify early lung cancers that can be treated with surgery and/or radiation. This research also allows for the continued collection of data and malignant lung tissue, which scientists throughout the U.S. can use for epidemiological studies on lung cancer, radon exposure, and tumor type. Data collected on the uranium miners during the past 33 years are being computerized for future statistical analysis. This research will provide valuable information on the effects of cigarette smoking and radon in relation to the development of lung cancer. Continued knowledge and understanding of lung tumorigenesis, improvement of diagnostic techniques in cytology and localization of lung tumors, and methodologies of choice in treating early lung cancer will result from this research. In addition, the conclusive data collected on the carcinogenic effects of cigarette smoking and radon can be used in establishing criteria for determining safe levels of radon exposure in industry and homes. (RPIS 10189)

University of Texas, Medical Branch at Galveston

Galveston, TX 77550

Department of Radiation Therapy

103. Cellular and Molecular Mechanisms in Radiation Carcinogenesis

R.L. Ullrich
(409) 761-4868

\$216,000

An assessment of cell and molecular events in radiation carcinogenesis is important to understand mechanisms and develop models for risk estimates. This assessment is particularly important for high linear energy transfer (LET) effects.

Current models are not adequate to explain experimental data, and sources of human data are lacking. This study compares cell molecular events in the carcinogenic process after exposure to neutrons and gamma-rays. This comparison allows researchers to determine similarities and differences as a function of LET. To determine these alterations, an in vivo/in vitro model system developed in this laboratory is being used to study murine mammary cancer development. These studies examine changes in tumor suppressor genes, proto-oncogenes, and growth regulatory mechanisms. Studies on tumor suppressor genes focus on the retinoblastoma and the p53 genes. Results of these studies lead to a better understanding of mechanisms of radiation carcinogenesis. Further, data derived facilitate the development of better models for risk estimates and provide insight into the applicability of experimental data to human risk estimates. (RPIS 10553)

University of Vermont
Burlington, VT 05405

Vermont Regional Cancer Center

104. The Development of In Vitro Mutagenicity Testing Systems Using T-Lymphocytes

R.J. Albertini
(802) 863-5716

\$275,000

The objectives of this research are to measure the induction of mutations at the hprt gene in human T-lymphocytes caused by exposure to irradiation sources and to characterize the molecular nature of the mutations. The mutations are being studied after both in vivo and in vitro exposure to the following agents: (1) external beam gamma irradiation (^{137}Cs source), (2) continuous beta irradiations delivered by yttrium-90, (3) Auger electrons and other low energy irradiations emitted by thallium-201, and (4) technetium-99m and ultraviolet light. The mutant frequency is being quantified by a cell cloning assay and determined by Southern blot analysis of the T-cell receptor gene rearrangement patterns of selected mutants. The hprt mutation event is being delineated by Southern blot studies to define the frequency of large structural alterations. These are being further defined by codeletion of x-linked probes and for deletion size pulsed field electrophoresis. The nondeletion mutations are being sequenced. Human heterogeneity with respect to these irradiations is being studied in vitro with blood samples from normal individuals, immunosuppressed transplant patients, patients with xeroderma pigmentosum (XP) and XP heterozygotes, and patients with ataxia telangiectasis (AT) and AT heterozygotes. (RPIS 9621)

University of Vermont College of Medicine
Burlington, VT 05405

Microbiology and Molecular Genetics Department

105. An Immunological Approach to the Study of DNA Repair

S.S. Wallace

(802) 656-2164

\$225,000

To measure the production and biological consequences of DNA base damage produced by ionizing radiation or oxidizing agents, immunochemical assays are being developed to quantitate unique modified bases in DNA. With the use of the appropriate chemically synthesized modified nucleotides conjugated to protein carriers, antibodies have been raised to thymine glycol, 5-hydroxy-5-methylhydantoin, dihydrothymine, and urea residues. These modified bases are representative of the radiolysis products of thymine. In an ELISA assay, thymine glycol and dihydrothymine can be detected in irradiated DNA at the femtomole level. Current studies are focusing on (1) looking at the immunochemical characterization of the antibodies in hand; (2) using the ELISA to quantitate the appropriate lesions in both x-irradiated DNA and in the DNA isolated from x-irradiated cells; (3) the developing monoclonal antibodies; and (4) the raising of new antibodies to modified cytosine and purine radiolysis products. (RPIS 9927)

Wake Forest University Bowman Gray School of Medicine

Winston-Salem, NC 27103

Department of Radiology

106. Direct Assays of Radiation-Induced DNA Base Lesions

K.T. Wheeler

(919) 748-6189

\$90,000

This grant examines the mechanisms by which ionizing radiation produces DNA damage. Dry, hydrated (2 of 32 water molecules/nucleotide) and solution salmon sperm DNA are irradiated under both O_2 and N_2 . The release of free bases is measured by high performance liquid chromatography, and the induction of base and nucleoside damage is measured by gas chromatography/mass spectroscopy. These studies provide important information on the types and quantities of DNA damage produced by the direct effect (direct ionization of the DNA or charge migration from ionized tightly bound water molecules) and the indirect effect (attack by hydroxyl radicals produced in the more loosely bound or free water). The hypothesis being tested is that the direct effect predominates when there are < 15 water molecules/nucleotide; the indirect effect becomes a significant contributor to the DNA damage when there are > 15 water molecules/nucleotide. (RPIS 9536)

University of Wisconsin Clinical Cancer Center

Madison, WI 53792

Human Oncology Department

107. Radiogenic Neoplasia in Thyroid and Mammary Clonogens

K.H. Clifton

(608) 263-5344

\$296,000

The goals of this study are to measure the risk of radiogenic cancer per target cell at risk in vivo and to determine the factors that influence the expression of radiogenic initiation in overt cancer formation. Quantitative transplantation bioassay procedures have been developed to (1) measure the concentrations of the clonogenic epithelial cells of rat mammary and thyroid glands under a variety of physiological conditions and following radiation exposure and (2) measure the frequency of radiogenic initiation of thyroid and mammary cancer per clonogenic cell in vivo in grafts of known numbers of surviving clonogenic cells. The project is to continue or initiate: (1) investigations of the kinetics of the total thyroid epithelial population and the clonogenic subpopulation during different goitrogenic regimens to determine the mechanisms of control of these populations; (2) studies of the hypothalamic-pituitary-thyroid axis in relationship to thyroid cell population kinetics; (3) investigate local cell/cell and hormonally mediated interactions during promotion/progression of radiogenic thyroid cancer; (4) design experiments to distinguish between the effects of total mammary clonogen numbers and clonogen proliferation on radiogenic mammary carcinogenesis with high and low linear energy transfer radiations; and (5) efforts to concentrate and further characterize the clonogenic cells. (RPIS 9630)

Radiation and Chemical Effects: Cellular and Molecular Biology

Intramural DOE Laboratories

Argonne National Laboratory
Argonne, IL 60439

Biological and Medical Research Division

108. Structural Studies of Site-Specific Mutants of the Photosynthetic Reaction Center

D.K. Hansen

(708) 972-3819

\$150,000

This project constructs and analyzes site-specific mutants of the photosynthetic reaction center, the only transmembrane protein for which a structure has been determined to atomic resolution. Study of this model membrane protein will help determine how the three-dimensional structure of an intrinsic protein complex is coupled to its function of producing a transmembrane charge separation that serves as the basis for the production of membrane potential.

The project constructs and analyzes site-specific mutants of the reaction centers of *Rhodobacter capsulatus* and *Rhodobacter sphaeroides* to determine the contribution of the protein side chains to electron transfer reactions between the prosthetic groups. Amino acids targeted for mutagenesis are those shown by the protein structure to be capable of interaction with the prosthetic groups by hydrogen bonding or van der Waals contacts, and thus have the potential to participate in the transfer of electrons through the reaction center. Studies address the mechanisms by which the protein modifies the chemical properties of its cofactors, especially the primary and secondary quinones, and how it contributes to the observed unidirectionality of electron transfer through the otherwise symmetrical reaction center complex. In addition, the project selects and analyzes spontaneous and induced second-site revertants of site-specific mutants as genetic tools for understanding interactions between the protein chains and prosthetic groups.

The effects of these mutations, both site-specific and compensatory, on the photosynthetic growth properties of the organism are assayed phenotypically, and genetic characterization of suppressor strains is used to determine that the sequence changes observed are indeed the ones that are both necessary and sufficient to restore photocompetence. Their effects on function of the reaction center in light-induced electron transport are investigated by using spectroscopy and computer modeling in collaboration with other investigators. (RPIS 5629)

109. Cellular and Molecular Mechanisms of Radiation-Induced DNA Damages

M.J. Peak

(708) 972-3850

\$218,000

The program objectives are as follows: (1) to investigate in biological systems the nature of the DNA lesions produced by a broad spectrum of cytotoxic, mutagenic, and carcinogenic environmental insults, especially ionizing radiation such as γ -rays and neutrons; and (2) to elucidate the chemical and metabolic mechanisms by which these lesions are produced, modified, and repaired. The program examines such diverse DNA lesions as single- and double-strand breaks, alkali-labile sites, pyrimidine dimers, DNA adducts, and DNA-protein crosslinks. This information is used to provide new insights into biological pathways and molecular mechanisms that produce these effects in response to radiation insults. One aspect of the study involves improving the technology of DNA damage analysis to gain more specific information than can be gained from currently available hydrodynamic assays. Improved understanding of the fundamental mechanisms through which genetically damaging lesions are produced, modified, or repaired provides the basis for (1) more accurate appraisals of current hazards from environmental insults, (2) improved techniques in managing ionizing and non-ionizing radiation used in medicine, (3) improved procedures to reduce or eliminate the effects of DNA lesions in humans, and (4) basic insights into molecular mechanisms of radiation carcinogenesis. (RPIS 1543)

Brookhaven National Laboratory
Upton, NY 11973

Biology Department

110. Control of Gene Expression in Mammalian Cells and Viruses

C.W. Anderson

(516) 282-3375

\$435,000

Gene expression in human cells is regulated and coordinated by posttranslational modifications of the proteins required for transcription, messenger ribonucleic acid (mRNA) processing, and the translation of RNAs. The primary reversible mechanism for regulation in mammalian cells is protein phosphorylation-dephosphorylation. To understand how gene expression is regulated and coordinated, the sites of protein modification must be identified, and the enzymes responsible must be purified and characterized. The small, well-characterized DNA tumor viruses, human adenovirus serotype 2 (Ad2) and simian virus 40 (SV40), are excellent model systems for analyzing gene expression. Human cells have a nuclear protein kinase that requires double-stranded DNA for its activity. This kinase (DNA-PK) phosphorylates proteins involved in DNA replication and transcription, including the large tumor antigen of SV40, the DNA-binding protein of Ad2, the cellular tumor-suppressor gene product p53, a DNA-binding autoantigen Ku,

and the heat-shock protein of 90-kDa. The major effort of this laboratory is directed toward characterizing DNA-PK and its substrates. The long-term biological consequences of radiation and other energy byproducts result from changes in gene expression. Knowledge of the way gene expression is regulated is essential to understand and predict these consequences and to develop methods to diagnose and treat human disease. (RPIS 1385)

111. Nucleic Acid Replication

J.J. Dunn

(516) 282-3012

\$220,000

This research focuses on the structure and interactions of macromolecules involved in the synthesis of bacteriophage T7 ribonucleic acid (RNA) and DNA. A major objective is to determine the molecular structure of T7 RNA polymerase. Work continues on the technicalities of obtaining crystals of T7 RNA polymerase, alone, and in association with its promoter sequence. The objective is to understand how this important enzyme initiates, elongates, and terminates RNA synthesis. Recombinant DNA technology is used, with genetic analysis, to map and express individual functional regions of the enzyme for biochemical and physical studies. These studies include detailed analysis of the role of T7 RNA polymerase in packaging replicated DNA. Other studies focus on the role of nucleic acid conformation and nucleic acid-protein interactions during transcription and DNA replication. The project is also involved in expressing in eukaryotic cells enzymatically active variants of T7 RNA polymerase containing additional amino acid sequences that cause the protein to localize in nuclei. These unique forms of T7 RNA polymerase are used to investigate how a high molecular weight, sequence-specific DNA binding protein becomes localized in nuclei and then interacts with a unique DNA sequence. This work adds to knowledge of specific and nonspecific nucleic acid-protein interactions in organisms with complex genomes, and helps clarify how eukaryotic regulatory proteins cross the nuclear membrane and then locate and distinguish their specific target sequence. (RPIS 0047)

112. Reactions of DNA Within Cells

S.A. Lacks

(516) 282-3369

\$205,000

The central importance of DNA as the genetic material of cells renders its reactions, both normal and abnormal, of general interest. Environmental pollutants may interact adversely with DNA to cause cell death or mutation, leading to disease. This project concerns cellular repair of DNA, DNA transport into cells, and the genetic basis of enzymes that act on DNA. The roles of nucleases that cleave DNA and of DNA methylation are investigated in cells of the genetically transformable Gram-positive bacterium, *Streptococcus pneumoniae*, and of Gram-negative *Escherichia coli*.

Specific research efforts include the following: (1) Mismatch repair. DNA mismatches can be repaired by a cellular

system that eliminates deleterious mutations. DNA cloning, sequencing, and transformation techniques are used to characterize the system. (2) DNA transport. The mechanism of donor DNA processing by membrane nucleases during DNA uptake is studied and its genetic implications determined. (3) DNA methylation. Strains of *S. pneumoniae* that differ in DNA methylation and contain one of two complementary restriction nucleases (one of which attacks only methylated DNA) are analyzed with respect to the genetic basis, regulation, and evolution of the restriction systems. (4) Plasmid transformation. Molecular mechanisms of genetic recombination in plasmid transfer, establishment, and transformation are examined in both *S. pneumoniae* and *Bacillus subtilis*. These include two novel effects: the ectopic integration of chromosomal genes and the chromosomal facilitation of plasmid transfer. (RPIS 0029)

113. The Roles of Proteinases in Normal and Abnormal Physiological Processes

W.F. Mangel

(516) 282-3373

\$250,000

The task objective is to study the role of proteinases, specifically plasminogen activators (PAs), in several normal and abnormal physiological processes. PAs, serine proteinases that cleave the serum zymogen plasminogen to the active protease plasmin, are involved in normal physiological processes such as fibrinolysis, cell migration, and tissue remodeling, and in abnormal physiological processes such as thrombosis and metastasis. More than one half of all deaths in the U.S. are attributable to defects in fibrinolysis and to metastasis. The proteins of the fibrinolytic enzyme system are studied by biochemical and biophysical techniques. New fluorogenic substrates are synthesized to assay enzyme activity. The unique facilities at the Brookhaven National Laboratory, the High Flux Beam Reactor, the National Synchrotron Light Source, and the Scanning Transmission Electron Microscope are used to define the structural changes that occur during regulation of enzyme activity. The goal is to understand how this enzyme system is regulated at the biochemical and biophysical level, and to use this information in the treatment of thrombosis and cancer. (RPIS 0013)

114. Radiation and Chemical Damage to DNA and Its Repair

R.B. Setlow

(516) 282-3391

\$235,000

Large scale power generation inevitably results in some environmental pollution by radiation or chemicals. Mutations resulting from exposures to the pollutants arise from changes in DNA, and there is extensive evidence that changes in DNA initiate events for neoplastic transformation. The responses of cells depend not only on the initial numbers of changes per unit length of DNA but on their persistence, and on the cellular replication and transcription machinery that reads them. This task measures radiation and chemical damages to cells of

vertebrates (e.g., human, mouse, fish). It also measures the kinetics of three types of repair—nucleotide excision, photo-reactivation, and dealkylation—and their consequences. The techniques used to measure repair are unscheduled DNA synthesis, susceptibility of DNA to nucleases specific for particular damages, loss of products from DNA, and stoichiometric transfer of an alkyl group from DNA to protein. Short-range goals are to determine how the various measures of DNA repair are associated with lifespan of a species, age of individual animals, and the variances in DNA repair among diseased and apparently normal populations. In general, the long-range goal is to correlate these measurements with DNA replication, cell survival, and mutation so as to estimate the hazards of deleterious agents by obtaining a molecular basis for constructing dose-response curves at low doses. A specific long-range goal is to determine quantitatively the effects of DNA damage to melanoma and retinoblastoma antioncogenes in hybrid fish with different numbers of copies of these genes. (RPIS 1285)

115. Nucleic Acid Structure

F.W. Studier

(516) 282-3390

\$290,000

Bacteriophage T7 and its host *Escherichia coli* provide an excellent system in which to study basic genetic processes. T7 contains a single molecule of linear DNA almost 40,000 base pairs long, whose complete nucleotide sequence is known. Processes such as entry of DNA into the cell, regulation of gene expression, replication and repair of DNA, genetic recombination, and assembly of virus particles are studied by genetic and biochemical techniques. The nucleotide sequence predicts that there will be 56 T7 proteins, and mutations affecting almost all of them have been found or constructed. Each T7 gene has been cloned so that it can be expressed during T7 infection or independently. These cloned genes, plus cloned fragments representing all parts of the T7 DNA molecule, are used in genetic analysis and manipulation of T7. A gene expression system based on the specificity of T7 ribonucleic acid polymerase for its own promoters is being used to produce individual T7 proteins for functional, biochemical, and structural analyses. This system is capable of expressing genes from a wide variety of sources and is used in many laboratories. Understanding basic genetic processes and structure-function relationships in T7 provides useful models and techniques for understanding genetic processes in more complex organisms. (RPIS 0019)

116. DNA Repair

B.M. Sutherland

(516) 282-3293

\$185,000

Sunlight damages DNA in human skin. DNA repair enzymes allow cells to circumvent the lethal, mutagenic, and oncogenic effects of DNA damage caused by solar radiation and by chemicals entering the environment. Understanding the cellular effects of ultraviolet (UV) and visible light is important both

in assessing potential hazards to humans from increased UV radiation resulting from depletion of stratospheric ozone and in determining the ability of human cells to withstand such damage. This program seeks to (1) measure the damage produced in cellular DNA in human skin by far UV- and near UV-radiation, and the ability of the cells to repair such damage; (2) evaluate the role of such damage in the production of cellular changes such as skin alterations, including cancer; and (3) characterize the repair enzymes involved in the cellular reaction to DNA damage. (RPIS 1824)

117. Eukaryotic Chromosome: Its Replication and Structure

J. Van't Hof

(516) 282-3419

\$125,000

The project has three facets. The first concerns chromosomal DNA sequences responsible for three replicon properties: replication initiation, replication termination, and time of replicon function in the S phase of the cell cycle (tempo-pause). The second is the structural organization of DNA and nucleoprotein within the metaphase chromosome. The third concerns the effects of damaged DNA on replicon properties and chromosomal structure. The specific objectives of the project are to (1) determine differences in structure and nucleotide sequence of DNA fragments that function as origins, termini, and tempo-pause determinants; (2) develop an in vitro replication assay system using plasmid constructs, containing an origin and termini from selected chromosomal replicons, to allow detailed analysis of how DNA damage affects the replicative functions of origins and termini; and (3) collaborate in the development of chromosomal preparations suitable for analysis by x-ray microscopy. The merits of the work are that it will characterize DNA in the genome that is essential for the propagation of genetic information, identify DNA responsible for gross genomic changes in older differentiated cells of multicellular organisms, and determine the usefulness of x-ray microscopy as a tool for structural analysis of chromosomes. (RPIS 0006)

University of California, San Francisco
San Francisco, CA 94143

Laboratory of Radiobiology and Environmental Health

118. Mammalian Cell Culture Systems for Molecular Studies of DNA, Mutagenicity, and Carcinogenicity

J.E. Cleaver

(415) 476-1636

\$641,000

Cultured mammalian cells proficient or deficient in various DNA repair and replication pathways are the basic biological systems used to determine how damage to chromatin, induced by environmental pollutants, eventually causes cell death, mutation, and cancer. Cells from patients deficient in excision repair of ultraviolet-light-induced DNA damage, and other radiation-sensitive mammalian cells, are used to measure

various parameters of DNA replication and DNA repair, to (1) determine the relationship of chromatin structure to repair and replication and (2) identify and clone DNA sequences that code for radiation and carcinogen sensitivity. A variety of shuttle vector systems are used to improve analysis of molecular events associated with DNA damage and repair as part of the basic biochemical approach of the laboratory's overall effort to uncover mechanisms of damage induced by energy-related environmental pollutants. (RPIS 1912)

119. DNA Replication and Repair

J. Cleaver

J. Murnane

(415) 476-3154

\$525,000

This program investigates how ionizing radiation and other DNA-damaging agents affect the organization, replication, and rearrangement of the genome in human and other mammalian cells. One approach is the characterization of cell lines containing mutations that result in sensitivity to ionizing radiation, including ataxia telangiectasia cells and the Chinese hamster cell line *irs1SF*, which was isolated in this laboratory. To clone the genes associated with these deficiencies, human DNA fragments have been selected that complement the ionizing radiation sensitivity. A human/cosmid DNA clone has been isolated that appears to contain all or part of a gene involved in ataxia telangiectasia, as demonstrated by *in situ* hybridization of these DNA fragments to the chromosome location 11q23, which has been identified as the locus for the gene(s) responsible for this disease. Another line of research in the laboratory involves the investigation of the mechanisms of DNA rearrangement in mammalian cells. These studies have addressed the question of why gene amplification, an important factor in cancer cell progression, commonly occurs after relocation of genes to new chromosome locations. A focus is how an initial DNA rearrangement, either spontaneous or induced by DNA damage, might influence the rate of recombination within the surrounding region. This is accomplished by analysis of rare integration sites that continuously demonstrate high rates of amplification and deletion after transfection of DNA into human cells. (RPIS 4455)

120. Embryo Cultures and Environmental Toxicity

R.A. Pedersen

(415) 476-3154

\$500,000

This program focuses on experimental approaches to mammalian organogenesis using the cultured mouse embryo as a model system. One objective is to determine timing of cell allocation to tissue and organ rudiments during early stages of organogenesis. This analysis is accomplished by microinjecting lineage tracers into single progenitor cells or by infecting progenitor cells with retrovirus, which encodes a histochemically detectable product. The tissue and organ distribution of marked descendants provides a fate map of the morphogenetic movements and differentiative decisions of embryonic cells during formation of the organ rudiments. This information is

essential to understand early organ formation and hence the etiology of environmentally induced birth defects. Another objective is to determine the molecular mechanisms of tissue and organ rudiment differentiation. Embryonic cells are analyzed to determine the mechanisms governing their behavior during gastrulation, when the body plan and organ rudiments are becoming established. In addition, cell-cell interactions are studied to characterize the nature of epigenetic information that regulates cell differentiation into specific tissues. This assessment is accomplished by analyzing the appearance of tissue-specific gene products under various experimental conditions. A third objective is to define the roles of genes involved in DNA repair by using homologous recombination in cultured embryonic stem cells to achieve germline alteration in the mouse. These activities provide the first detailed view of how the mammalian embryo develops during organogenesis stages. Such information should have important implications for the prevention or amelioration of birth defects in humans. (RPIS 4460)

121. Biochemical Functions of Macrophages in Pulmonary Damage from Environmental Pollutants

Z. Werb

M. Banda

(415) 476-4622

\$520,000

This program focuses on the actions and interactions of the extracellular matrix, scaffolding of tissues, the cells delimiting these tissues, and the migratory cells of the host defense systems. Because of the inherent sensitivity of the cellular components of the hematopoietic and immune systems and of connective tissue cells, or because of their intimate involvement in host defense mechanisms, these interrelated cellular systems are prime targets for radiation and other toxic agents produced during energy generation. One major area of investigation concerns cells, especially mononuclear phagocytes, that mediate the acute and chronic inflammatory response and repair processes. These studies are primarily directed toward characterizing the molecular properties and regulation of secreted proteins that participate in these host defense responses. An understanding is developing of how macrophages interact with fibroblasts and endothelial cells through the mediation of macrophage-derived polypeptides such as angiogenesis factors, growth factors, chemotactic factors, and interleukin-1, and how these processes are perturbed by inflammation and by chemical substances such as tumor promoters. The project is identifying the macrophage gene products expressed *in vivo* and reconstructing the roles that these products play *in vivo*. A related area is the remodeling of the extracellular connective tissue environment of cells and the factors that control the balance between biosynthesis and breakdown during development, growth, repair of injuries, and oncogenic transformation. The approaches to this area are cellular, molecular, and genetic, with emphasis on the phenotypic expression of metalloproteinases and endogenous metalloproteinase inhibitors. (RPIS 2791)

Lawrence Berkeley Laboratory Berkeley, CA 94720

Cell and Molecular Biology Division

122. Molecular Carcinogenesis: Molecular Mechanisms Underlying Tissue-Specific Gene Expression

M.J. Bissell

(510) 486-4365

\$790,000

The major aim of this task is to understand the molecular mechanisms underlying how a cell becomes specialized and how it remains functionally normal, information that will be useful in understanding mechanisms in aging and disease. The choice of the culture system for studies of gene expression bears a crucial and direct relation to the relevance of the results obtained. The mammary gland is well suited for such studies because these cells can now be induced to differentiate with precision in tissue culture. Researchers also have specific molecular markers to ask a number of fundamental questions. Scientists now have succeeded in producing complete functional "alveoli" with capacity for vectorial secretion. In the biochemical capabilities (including the capability for vectorial secretion) these alveoli bear an uncanny resemblance to the alveoli of the lactating gland. It has been shown that in the cases where functional differentiation is induced in the absence of exogenous basement membrane (bm), there is endogenous elaboration of bm, the appearance of which correlates precisely with increase in milk production. Significant recent advances include the isolation of a cell strain that is ECM- (extracellular matrix) and hormone-responsive, that can be stably transfected and the demonstration that bovine and rat β -casein genes (attached to chloramphenicol transaminase) contain sequences that are dramatically regulated by substratum. It is believed that there may indeed be an ECM response element; experiments to prove this are underway in collaboration with the Monsanto Company. In addition, researchers now have clear evidence that embedding cells in bm can induce milk protein expression in the absence of cell-cell interaction and polarity. Thus ECM, in conjunction with hormones, is necessary to direct transcription of tissue-specific genes, a finding of fundamental importance also for expression of foreign genes (RPIS 3228)

123. Mitotic Recombination and DNA Repair

M.S. Esposito

(510) 642-4863

\$90,000

Chromosomal recombination in both mitosis and meiosis are important aspects of eukaryotic DNA transactions related to human health. Recombination occurring in somatic cells is a major route for repair of chromosomal damage implicated in cancer etiology and is involved in development of the immune system. The long-term goal of this research is to contribute to understanding the molecular mechanisms of chromosomal recombination in mitosis and meiosis of eukaryotic organisms. The experimental program involves phenotypic genetic analysis

of hyporecombination (*rec1-1*, *rec3-1*, and *rec4-1*) and hyperrecombination (*rec46-1*) mutants of *REC* genes of *Saccharomyces cerevisiae* and genetic mapping, molecular cloning, and DNA sequencing of certain *REC* genes identified in the Lawrence Berkeley Laboratory whose mutations confer drastic mitotic and meiotic phenotypes. Computer analysis will be employed to compare the primary structure of *REC* proteins to polypeptide sequences of any known function. This information will be used to formulate hypotheses regarding the roles of *REC* proteins in recombination. *REC*-fusion proteins will be purified to homogeneity by immunoaffinity chromatography and assayed for biochemical reactions implicated in genetic recombination and DNA repair. In vitro assays of DNA strand transfer employing temperature conditional hyporecombination mutants (*rec1-1*, *rec3-1*, and *rec4-1*) indicate that the *REC1* gene controls a yeast DNA strand exchange protein required for general recombination, repair of x-ray damage, homothallic mating type switching, and meiosis. The researchers have purified the wild type *REC1* and mutant *rec1-1* DNA strand exchange proteins to near homogeneity and have demonstrated that the mutant protein is thermolabile in vitro. The *REC1* protein is the first example in yeast of a *RecA*-like protein required for recombination and repair. Gene cloning and gene disruption will be employed to determine whether *REC1*, *REC3*, *REC4*, or *REC46* are essential genes and to generate null alleles of nonessential genes. Because all four *REC* genes are required for normal meiosis and sporulation, their mutant alleles will be analyzed for effects upon the progress of meiosis, recombination, and chromosomal stability during meiosis. (RPIS 3822)

124. Genetic Study on Yeast

R.K. Mortimer

(510) 642-4131

\$210,000

For the past several years, the activities of these researchers have been centered on gaining an understanding of a set of eight recombinational repair genes in the yeast *Saccharomyces cerevisiae*. The principal mutant phenotypes of these genes are sensitivity to ionizing radiations, recombination deficiencies, and meiotic abnormalities. The researchers have mapped all of these genes and have cloned and sequenced several of them. It has been shown that at least two of these genes are inducible by DNA damage; the researchers have identified a 29 base pair sequence needed for induction of one of them. Some of the mutants in this set of genes are blocked in the repair of DNA double strand breaks: the researchers are using pulsed-field gels to study the phenomenon. In addition to these activities, the researchers have assumed the responsibility of collating all the genetic mapping data for yeast for several years. A compilation appeared in 1989, with the most recent version scheduled for 1991. Related to these studies is recent work on genetic interference. The researchers have developed a reasonable model of this phenomenon and have tested this model against data from yeast and drosophila with very encouraging results. The researchers also maintain and operate the Yeast Genetic Stock Center, which is used by hundreds of investigators worldwide. (RPIS 0116)

Chemical Biodynamics Division**125. Center for Biomolecular Design***P. Schultz**(510) 486-4333**\$150,000*

The Center for Biological Design at Lawrence Berkeley Laboratory (LBL) bridges chemical science, biological science, and computer science by combining the expertise in LBL and the University of California-Berkeley. The Center catalyzes an interdisciplinary approach toward chemical biology and computational biology that merges a detailed understanding of biological systems with the ability to analyze and manipulate chemical structure. The project is redesigning the biological molecules to create new classes of novel biomolecular structures with applications to major problems in the medical, biological, and environmental sciences relevant to DOE missions.

Examples of new technologies emerging from interdisciplinary studies at LBL include designing and creating a new generation of biopolymers that have unique properties and redesigning natural proteins to create new properties. One example of the latter is catalytic antibodies tapping the tremendous diversity ($>10^{10}$ molecules) and specificity of the immune system to create "custom made" catalysts. These molecules may lead to restriction enzymes for proteins and sugars for novel therapeutic agents for destroying cancer cells, viruses, or even atherosclerotic plaques. Chimeric receptors have been constructed that "reprogram" the transmittal of information to cells. This research aids the therapy and understanding of disease including memory dysfunction and may ultimately lead to novel cellular-based sensory or memory devices. Proteins from organisms that function under extreme conditions of pressure, temperature, and pH (extremophiles) are isolated and characterized. These proteins are redesigned to create new proteins with new catalytic properties functioning under extreme conditions and environment. Powerful methods have been developed making it possible to generate proteins that contain synthetic amino acids with novel properties not limited to the natural 20 amino acids. These activities reflect the tremendous chemical potential inherent in the complex architecture of biomolecules. (RPIS 5617)

**Lawrence Livermore National Laboratory
Livermore, CA 94550****Biomedical Sciences Division****126. Chromatin Structure in Mammalian Sperm***R.L. Balhorn**(510) 422-6234**\$360,000*

The DNA of mammalian sperm is packaged by small arginine-rich proteins (protamines) in a unique fashion, one that renders all its genes inactive and the DNA biochemically inert. Several recent studies have suggested that defects in protamine expression and function adversely affect fertility and early embryogenesis. Protamine damage, resulting from the exposure of males to toxic chemicals has also been correlated to early fetal death. This study employs a variety of biochemical and physical techniques to identify the structure of sperm chromatin in mammals and elucidate the DNA-protein and protein-protein interactions essential for normal sperm function. Nuclear magnetic resonance and laser Raman spectroscopy, chemical crosslinking studies, and automated protein sequence analysis are being used to identify the conformation of protamines 1 and 2 in vivo and define how the two proteins interact with each other and DNA. Scanning tunneling and atomic force microscopy are being used to examine the physical structure of synthetic DNA-protamine complexes and investigate how the individual fibers of DNA are packed around the nucleus. High resolution computer graphics are being used to integrate this information and model the three-dimensional structure of sperm chromatin. Future transgenic mouse studies will employ protamine genes altered by oligonucleotide-mediated mutagenesis to determine how protamines are incorporated into sperm chromatin and to examine what features of protamine structure and function are essential for fertility and the progress of early embryogenesis. (RPIS 0266)

127. Molecular Mechanisms of Mutagenesis: An In Vitro Glycophorin A-Based Cellular Model*W.L. Bigbee**(510) 422-5682**\$150,000*

The purpose of this project is to develop an in vitro mutation assay system using a cell line that expresses human glycophorin A. Model systems being explored include human erythroleukemia cells, mouse erythroleukemia cell/human chromosome 4 hybrids, and rodent cells transfected with glycophorin A cDNA expression plasmids. Using this system, the project is applying recent developments in the field of molecular genetics, recombinant DNA technology, and mutagenesis to study the mechanisms of spontaneous, chemical-, and radiation-induced genetic damage. Monoclonal antibody labeling and flow sorting are being used to immunoselect variant cells which have lost expression of one glycophorin A allele in a manner analogous to the method used by another project to identify glycophorin A variant human erythrocytes arising in vivo. The knowledge gained is being used to evaluate the

biological significance of damage induced in human somatic cells and gain understanding of the spectrum of genetic alterations that result in erythrocytes of variant phenotype arising in vivo. Variants are being cloned and analyzed for genetic alterations at the glycophorin A locus. Fluorescence in situ hybridization, RFLP, and Southern blot analysis will be used to identify mutants arising by chromosome loss, mitotic recombination, or by deletions and rearrangements. The polymerase chain reaction, enzymatic method for specific amplification of selected DNA and messenger ribonucleic acid sequences is being developed for analysis of base sequence alterations. (RPIS 5182)

128. Human Mutagenesis: Methods, Applications, Animal Models, and Mechanisms

R.G. Langlois

(510) 423-5765

\$370,000

This project is developing analytical methods for detecting and characterizing human in vivo somatic cell mutations utilizing new developments in cytochemistry, analytical cytology, and molecular biology. Monoclonal antibodies are being developed for allele-specific immunofluorescent labeling of glycophorin A (GPA) and major histocompatibility (MHC) proteins, and for cell lineage-specific markers. Flow sorting and immunoaffinity separation methods are used to purify variant phenotype cells for characterization of mutational damage at the molecular level. The development of the GPA assay for in vivo somatic cell mutations in humans to reticulocytes is extended to provide molecular characterization of variant cells at the mRNA level. Development of mutation assays utilizing the MHC loci in humans and animal models allows interspecies and intertissue comparisons of mutational mechanisms. The GPA assay is applied to exposed and unexposed populations to characterize the mechanisms of mutation induction and expression and to identify atypical individuals for collaborative multi-endpoint studies. Such studies provide the potential for understanding the mechanisms and health consequences of interindividual variability in susceptibility to genetic damage. (RPIS 0259)

129. Human Germinal Gene Mutation Project

H.W. Mohnenweiser

(510) 422-0534

\$260,000

The goal of this project is the development and subsequent validation of the methods necessary to estimate the germinal gene mutation rates in human populations exposed to genotoxic agents. The developing molecular techniques being used to study gene structure have potential to generate significant quantities of data on genetic variation from each offspring studied and thus to provide the tools necessary for estimating the heritable mutation rate in human populations. Efforts thus far have focused on developing DNA-based methods for detecting two types of molecular lesions. The primary screen for insertion, deletion, and/or rearrangement mutations is a modified restriction-enzyme-site-mapping strategy using both unique sequence and tandem-repeat-element probes.

Polymerase chain reaction (PCR) amplification plus high resolution electrophoresis is being employed to screen for length variants in micro-repeat segments. The heteroduplex mapping approach employs denaturing-gradient-gel-electrophoresis of PCR amplified genomic DNA duplexes to detect nucleotide substitutions. Feasibility studies involve screening of DNA from in vitro mutagenized (ethyl nitrosourea or radiation) somatic cells as prototypes for human probands. Efforts are focusing on increasing the portion of the genome screened and increasing the efficiency of the data acquisition. Collaborative studies have been initiated to utilize these methods to determine the induced germination rate in mice. Characterization of the mutants recovered in these experiments will provide an understanding of the mechanisms of mutant induction and the potential existence of mutagen molecular "fingerprints." Quantitation of the frequency of the germinal gene mutations in human populations will provide data to address one of the significant issues for humans, namely, the component of the genetic burden and health risk transmitted to future generations that is caused by exposure to mutagenic agents. (RPIS 4720)

130. Molecular Genetics of DNA Repair

L.H. Thompson

(510) 423-5658

\$680,000

The objective of this project is to characterize genes involved in repairing DNA damage from environmental agents in human and rodent cells. Because repair processes are a major determinant of the biological effects of DNA damage (cell killing, mutation, etc.), it is essential to gain understanding of repair processes at the molecular level. By analyzing repair-deficient mutants of rodent cells, which can be corrected with genes from normal human cells, the researchers are mapping, isolating, and characterizing these human DNA repair genes. The human repair XRCC1 and ERCC2 genes and their encoded proteins are being characterized. XRCC1 is the only cloned mammalian gene that affects sensitivity to ionizing radiation, and it is involved in repairing DNA single-strand breaks. ERCC2 is a nucleotide excision repair (NER) gene that is essential for repairing ultraviolet and bulky-adduct damage. The protein coding regions of both genes in the form of cDNA "minigenes" are being used to overexpress the repair proteins for isolation and biochemical analysis. The role of these proteins in repair is being studied, including the molecular basis of sister chromatid exchange, which is controlled by XRCC1. ERCC2 is being used to test for correction of the defects in cells from human cancer-prone disorder *xeroderma pigmentosum* (XP). XRCC1 and ERCC2 are being used to make transgenic mice deficient in these loci, providing models for XP and other human repair disorders. Major steps in this process include (1) isolation of both mouse XRCC1 genomic and cDNA sequences that will be used for targeted mutagenesis in mouse embryonic stem cells, (2) construction of an improved minigene of ERCC2 that effectively corrects the Chinese hamster ovary UV5 mutant, and (3) regional chromosomal mapping of the ERCC2 NER gene to human chromosome 16p13.13. (RPIS 0261)

131. Flow and Analytical Cytogenetics*B.J. Trask**G.J. van den Engh**J.N. Lucas**(510) 422-5765**\$765,000*

This work consists of three projects: flow cytogenetics, the flow cytometry core facility, and analytical cytogenetics.

The purpose of the flow cytogenetics project is to develop the means and methods for flow karyotyping and chromosome sorting. These skills are being applied to a variety of areas related to genomic research, medical diagnostics, and dosimetry. Chromosomes purified by flow sorting are used for the production of cloned or polymerase chain reaction amplified DNA libraries. Numerical methods for flow karyotype analysis are being developed to compare karyotypes and optimize sort purity and throughput. Studies that apply flow cytometry to the analysis of chromosome polymorphisms and deletions and to the characterization of complex karyotypes will be extended. Methods for a standardized representation of flow karyotypes are being developed. Chromosome recovery and DNA quality after sorting are being optimized. The flow cytometry technology is replicated for use in a broader range of biological applications as a flow cytometry core facility.

The flow cytometry core facility provides flow cytometry and cell sorting instruments to the Livermore Biomedical Sciences Division. The flow core designs, tests, and maintains instruments and makes them available to the division investigators. The core collaborates with industry and academic groups to apply the skills and knowledge acquired during the development process to research areas not covered by the Biomedical Sciences Division.

The analytical cytogenetics project develops and applies fluorescence in situ hybridization to the detection and quantification of the cytogenetic aberrations in metaphase spreads and interphase nuclei. Two classes of probes are being developed and evaluated: (1) repeat sequence probes for chromosome enumeration and discrimination between translocations and dicentrics and (2) whole chromosome probes for structural aberration detection. These probes are being applied to quantify residual genetic damage (i.e., translocations) in the peripheral blood lymphocytes of individuals as an indication of radiation exposure level. Multicolor computer-assisted fluorescence microscopy is being developed to support these studies. (RPIS 3937)

132. Detection of Gene Mutations and Chromosomal Abnormalities in Human Sperm*A.J. Wyrobek**(510) 422-6296**\$175,000*

The purpose of this research is to develop methods for detecting germinal mutations (gene mutations and aneuploidy) in human sperm, to characterize the molecular lesions of mutant sperm sorted by flow cytometry, and to investigate the induction and persistence of germinal mutations in men exposed to mutagenic agents, especially agents related to energy technology.

Mutations in male germ cells contribute substantially to the incidence of aneuploidy and de novo gene mutations detected in human newborns, but there exist no efficient methods for detecting spontaneous or induced germinal mutations in sperm. The project has developed a procedure to decondense human sperm chromatin for reliable fluorescent in situ hybridization with chromosome-specific DNA probes. Protocols are being developed to detect sperm carrying the major aneuploidies observed at birth, especially sex-chromosomal aneuploidy. The project has demonstrated that human P2, like P1, is encoded by a single copy gene—a finding crucial to detection of null mutations at these loci—and has identified DNA segments of the messenger ribonucleic acid that may be involved in translational regulation and processing of protamines. Flow-cytometric detection of fluorescently tagged monoclonal antibodies (MABs) has been used to identify rare human sperm that have lost or altered their expression of either of two protamines, P1 and P2. The project has surveyed 44 semen samples from 4 healthy donors and measured frequencies of approximately 7 and 17 sperm per million that did not bind with MABs specific for P1 or P2, respectively. Variant nuclei were sorted by flow cytometry and have the size, DNA content, and appearance of normal sperm nuclei, though they are slightly rounder in shape on average. The project is focusing on investigation of the molecular lesions of individually sorted variant nuclei using immunological labelling, accelerator-mass spectroscopy, and the polymerase-chain reaction. It is also obtaining semen samples from cancer patients to determine if mutagenic drugs elevate the frequencies of variant sperm. (RPIS 4220)

Los Alamos National Laboratory**Los Alamos, NM 87545****Life Sciences Division****133. Control of Cell Cycle and Transformation***E.M. Bradbury**(505) 667-2690**\$516,000*

In lower eukaryotes, the *cdc2* gene has been shown to serve as a key cell cycle regulator that controls commitment to DNA replication and the onset of mitosis. The product of the control gene *cdc2* is a ser/thr kinase that, when activated, phosphorylates a series of cellular substrates essential for progression through these critical decision point locales within the division cycle. Because of growing interest in the role this gene plays in regulating proliferation in higher eukaryotes, this project employs cultures of human diploid fibroblasts, their transformed derivatives, and the FT210 mouse cell line (which possesses a temperature-sensitive lesion in its *cdc2* gene) to (1) identify and characterize kinase-mediated regulatory mechanisms within the mammalian cell cycle, (2) measure the kinetics and activation of kinases (and associated phosphatases) throughout the division cycle, (3) characterize the spectrum of cellular substrates phosphorylated by these kinases at major cell cycle decision points and the sequence in which the substrates are phosphorylated, and (4) determine the effects of neoplastic

transformation on kinase-mediated regulatory mechanisms. Recently, in collaboration with U.C., Davis, the study (1) demonstrated the existence in normal cells of kinase-mediated regulation of commitment to DNA replication, a regulation that is lost during conversion to the neoplastic state; (2) found that kinase-mediated mechanisms involved in the G2 phase are conserved in both normal and transformed cells; (3) demonstrated that at least three major *cdc2*-encoded kinases in mammalian cells differ in both subunit composition and levels of activity at different stages of the cell cycle, and (4) developed techniques for synchronizing the growth of human and FT210 cells at multiple stages of the cell cycle. These experimental approaches allow a far better understanding of the genetic and molecular bases for regulation of mammalian cell proliferation. (RPIS 4716)

134. Molecular Genetics of Radiation Repair Genes

D.J. Chen

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\$400,000

The objective of this program is to use somatic cell genetics and recombinant DNA technology to study the molecular mechanisms of ionizing radiation-specific DNA repair in human cells. The ultimate goals are to isolate the human genes involved in repairing DNA damage caused by ionizing radiation and to study the expression of the repair genes in human cells. The specific aims are to (1) determine how many genetic loci are involved in repairing ionizing radiation damage, (2) develop efficient molecular cloning strategies for cloning human ionizing-radiation repair genes, and (3) map repair genes in the human genome. This approach provides a method for identifying repair proteins and provides a starting point for studies on repair responses to ionizing radiation damage. (RPIS 5181)

135. Chromosome Structure and Function

L.L. Deaven

(505) 667-3114

\$170,000

This project is designed to provide new information about the relationships between chromosome damage and chromosome function. A number of physical and chemical agents associated with energy production alter chromosome structure or induce changes in the chromosome number of normal mammalian cells. These studies are designed to document these changes and to elucidate the cellular responses to their initiation and perpetuation. The major approach to achieving these aims involves improving flow cytogenetic analysis. Pure fractions of human chromosomes are essential for the construction of chromosome-specific DNA libraries and may prove to be a critical element in the assemblage of a physical map of the human genome. Chromosome libraries and a physical map of the human genome will provide a new generation of tools for detecting chromosomal changes and correlating these changes with disease. Therefore, these researchers are attempting to optimize the production of pure fractions of chromosomes through improvements in chromosome isolation, handling of isolated chromosomes, and detection of purity levels in sorted

chromosomes. Closely related studies in radiation cytogenetics, gene mapping, and in situ hybridization with fluorescently labeled DNA probes are also continuing. These studies will contribute to the growing body of knowledge about chromosome physiology, which in turn will help to define the health consequences of chromosome aberrations in humans. Chromosome damage analysis is a reliable biologic dosimeter that can be applied to humans. Unfortunately, the health implications of chromosome damage are not fully understood. This understanding will only be made available through research into chromosome structure and physiology. Accordingly, this project continues to attempt to provide useful information toward a better understanding of the cellular effects of chromosome damage. (RPIS 4457)

136. Molecular Biology of Cell Cycle Dependent Genomic Structure

L.R. Gurley

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\$610,000

The objective of this program is to identify those constituents and biochemical processes in chromatin that, when altered or damaged, may result in neoplasia. To accomplish this objective, the researchers have developed new analytical methods for flow cytometry (FCM), high performance liquid chromatography (HPLC), and high performance capillary electrophoresis (HPCE) that help determine how various byproducts of energy technology interact with chromatin. Following exposure of cells to radiation and toxic chemicals, these new analytical methods are used to determine the modifications in chromatin structure that lead to transformation and changes in cell proliferation. First, FCM sorting is used to isolate normal and neoplastic subpopulations of cells. Then, these cells are used for HPLC and HPCE analysis of alterations in nucleoproteins that are related to chromatin structural changes. Finally, sorted viable cells are examined in culture to determine if and when malignant characteristics are manifested following treatment with radiation and toxic agents. In this way, the changes in chromatin composition related to chromatin structural changes and carcinogenetic events are identified. These activities are expected to establish a factual basis for the hypothesis that cell proliferation and metabolism are regulated through modulations of chromatin structure and that these modulations are controlled by alterations in the complex interactions between DNA and nucleoproteins that are driven by chemical modifications of nucleoproteins such as phosphorylation and acetylation. Results from this program should lead to the (1) identification of chromatin targets sensitive to attack by radiation and toxic chemicals, (2) identification of molecular structural alterations in chromatin leading to chromosome damage, (3) formulation of a model for the biochemical mechanisms of damage by radiation and toxic agents, and (4) development of new techniques for damage assessment. (RPIS 5641)

137. Karyotype Instability and Neoplasia Studies*P.M. Kraemer*

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\$300,000

The common solid tumors of humans result from the accumulation of multiple base and chromosome mutations. These mutations affect numerous genes in each tumor and are acquired sequentially during tumor progression by iterative rounds of variation, proliferation, and selection. The mutated genes are of several categories, including the much studied oncogenes and tumor suppressor genes that are directly involved in producing the neoplastic phenotype. However, the process appears to be driven by another kind of mutation, which is a heritable loss of genomic stability. This instability is commonly manifested by ongoing chromosome changes. Finally, cellular senescence becomes limiting during the iterative rounds of selection that occur in tumor progression and hence the mutation known as immortalization is required. The long-term goal of this research project is to determine the molecular mechanisms and identify the genes involved in chromosomal instability and immortalization. Candidate genes for a role in chromosomal stability include those whose gene products are normally involved in genome and chromosome organization such as topoisomerase II or nuclear matrix/scaffold proteins. A search for mutations in these genes in neoplastic cells is taking place. It has been shown that SV40 T antigen is a direct clastogen when expressed in human cells but that T antigen does not directly transform or immortalize these cells. The SV40/human fibroblast model is used to study the mechanisms of chromosomal instability and its relationship to carcinogenesis. (RPIS 4713)

138. Pulmonary Damage*B.E. Lehnert*

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\$660,000

The lung's pulmonary macrophage population consists of several subpopulations that can be defined by their anatomical locations and/or by other biophysical, biochemical, and functional criteria. Of these subpopulations, the alveolar macrophages have received the most experimental attention in the context of lung defense and repair mechanisms. However, major gaps in the knowledge of alveolar macrophage involvement in these important processes continue to persist. Moreover, roles in lung defense and lung repair played by other subpopulations of pulmonary macrophages are currently unknown. Accordingly, the major objectives of this task are (1) to elucidate pulmonary macrophage-associated mechanisms involved in the clearance and retention of particles that deposit in the lung and (2) to delineate cellular and molecular mechanisms by which pulmonary macrophages regulate lung fibroblast activities during exaggerated lung repair, as observed in pulmonary fibrosis induced by the inhalation of fibrogenic particles. These areas of investigation, which use both *in vitro* and *in vivo* model systems, have been made possible by recent accomplishments at Los Alamos National Laboratory including the successful isolation of purified subpopulations of viable

pulmonary macrophages, and, more recently, the isolation of resident lung fibroblasts using advanced cell separation strategies that utilize multiparameter flow cytometry. (RPIS 4714)

139. Mechanisms of Radiation and Chemical Genetic Toxicology*G.F. Strniste*

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\$750,000

This program determines molecular mechanisms by which radiation and environmental chemicals induce heritable genetic change. A team research effort focuses toward understanding metabolic processes involved in the recognition, processing, and/or fixation of DNA damage. Research objectives include (1) isolation and characterization of the ERCC5 human DNA excision repair gene and its encoded protein, (2) elucidation of the role of this protein in maintaining cellular resistance to genotoxic agents, (3) molecular definition of gene mutation induced in human cells by low doses and low dose rates of ionizing radiation, and (4) *in vitro* modeling of genetic recombination. Progress includes (1) isolation of functional ERCC5 complementary DNA (cDNA) clones via cDNA-cosmid recombination and partial sequencing of several of these clones, (2) regional mapping via *in situ* hybridization of ERCC5 to position q31.3-q33 on human chromosome 13, (3) application of polymerase chain reaction/denaturing gel electrophoresis in the analysis of mutational spectra in human cells induced by ionizing radiation, and (4) refinement of unique shuttle vector systems to examine mutation, genetic recombination, and preferential gene excision repair. The significance of this research is increased understanding of the relationship between the action of genotoxins on DNA and the processing of induced damage to the expression of altered phenotype including neoplasia. Research areas include (1) definition of the physical and enzymatic properties of the ERCC5 repair protein, (2) physical and biochemical assessments of ERCC5 protein interactions with DNA damage in native chromatin, (3) expansion of the current database on ionizing radiation-induced genetic mutational spectra with emphasis on low dose rate exposures, and (4) elucidation of the mechanism(s) mediating the induction of genetic recombination. (RPIS 4717)

140. Regulation of Mammalian Cell Proliferation

W. Wharton

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\$210,000

These studies provide a basic understanding of the mechanisms by which growth factors regulate proliferation in normal cells and identify alterations in specific regulatory steps that can lead to neoplastic transformation. The specific factors that control the initiation of DNA synthesis are identified. In addition, various aspects of receptor processing that play a role not only in the regulation of cell cycle traverse but also in earlier events such as the induction of specific genes are described. A discrete regulatory step under hormonal control in normal cells that appears to be abrogated during an early step of transformation is also described. Studies using cell hybrids have more closely defined the control of these processes. This study is extended by these methods: (1) continuing the investigation of cellular proteins and ribonucleic acids expressed at well-defined stages of the cell cycle, (2) investigating the role of hormone receptor processing in the generation of regulatory events that control cell cycle traverse, and (3) developing an experimental system that allows genetic analysis of the regulation of cellular growth. Understanding the molecular events that control the growth of normal cells provides information concerning the physiological hemostatic mechanisms. (RPIS 2682)

Oak Ridge Institute for Science and Education

Oak Ridge, TN 37831

Medical Sciences Division**141. Microbiology**

H.I. Adler

(615) 574-1222

\$50,000

Genetic studies in micro-organisms are useful for developing concepts and methods applicable to higher organisms. This study focuses on genes that control sensitivity to oxygen and its toxic byproducts. All organisms develop ways of coping with the toxic effects of oxygen. Available data suggest that this is accomplished similarly in organisms as diverse as bacteria and humans. The project maps and isolates genes that have oxygen protective functions. Initially, a group of 15 oxygen-sensitive mutants of *Escherichia coli* is being studied. The *E. coli* mutants are useful because of the genetic techniques available for manipulating genes in this species. It is anticipated that the determination of the structure and function of genes controlling oxygen sensitivity in microorganisms will facilitate the understanding of this important group of genes in higher organisms. In addition, it is becoming increasingly important to understand oxygen sensitivity in micro-organisms because of the role played by anaerobes in processes such as fuel production and waste remediation. (RPIS 5426)

142. Alterations in Lipid Metabolism, Cell Mediators, and Membranes in Disease

F. Snyder

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\$450,000

The broad aim of this research concerns the function of lipids as components of membranes and as cellular mediators of inflammation and other hypersensitivity reactions in mammalian cells. Attention is also focused on the mechanism of action of a new group of phospholipid analogues of platelet activating factor (PAF) that possess selective antitumor properties with inhibitory activities against the membrane budding of the AIDS virus and subsequent replication. The cytotoxic actions of these antitumor lipids are targeted on the surface membrane rather than on the cell nucleus as are other conventional chemotherapeutic drugs. Bioactive lipid mediators such as PAF and arachidonic acid metabolites provoke severe cellular reactions that cause serious impairment of respiratory, hematopoietic, cardiovascular, and renal functions. A major effort focuses on how membrane lipids function as both structural components and precursors of potent second messengers that can trigger cellular signal transduction events. This research addresses pertinent DOE issues on the important role of lipids in (1) burn injuries and altered functions of hematopoietic cells induced by radiation and (2) adverse inflammatory, respiratory, and immune responses resulting from accidental or environmental exposure to energy-related biohazards. Potential applications include testing the usefulness of anti-PAF and antieicosanoid receptor antagonists and/or enzyme inhibitors as drugs for treating radiation injuries and toxicant-induced inflammatory disorders. Molecular biology techniques are used to investigate the regulatory controls and active catalytic sites of key enzymes that catalyze rate limiting steps in the formation of PAF and related ether-linked glycerolipid membrane components. This research program is renowned internationally for its important contributions in PAF/lipid research and for the technology transfer of methodology and results to the pharmaceutical industry and clinical medicine. (RPIS 1923)

Oak Ridge National Laboratory

Oak Ridge, TN 37831

Biology Division**143. Regulation of Membrane Transport**

J.S. Cook

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\$250,000

This group uses mammalian cells in culture as model systems to investigate the dynamics of cell surface membranes and the regulation of their transport systems in response to various stimuli. Its projects include (1) molecular biological analysis of differentiation in cultured kidney cells with emphasis on the mechanisms by which the parent cells, proximal tubules, in vivo reclaim glucose from the glomerular filtrate and thereby prevent loss of sugar in the urine and (2) responses (both

activation and induction) of transport systems characteristic of proliferating cells following treatment of quiescent cells with epidermal growth factor (EGF). The latter project includes an analysis exploiting site-specific mutants of EGF. (RPIS 2368)

144. Effects and Uses of Chromosome Aberrations

W.M. Generoso

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\$100,000

Heritable mutations and transmissible chromosome aberrations that arise in mouse mutagenesis studies provide valuable material for indepth investigations, including DNA-mapping studies. This program contributes cytogenetic analyses of rearrangements in mitotic (G-banded) and meiotic chromosomes (synaptonemal complexes). Also studied is the organismic expression of certain chromosome rearrangements, as well as the events that play a role in the transmission of aberrations to subsequent generations. The findings are of considerable basic interest; they are also needed for assessments of genetic risk, because they complement data on the frequency of induction. Where rearrangements are associated with phenotypes, this occurrence enhances opportunities for structure-function correlations, especially where molecular analysis of breakpoints is possible. Several rearrangement-associated phenotypes (neurological, morphological, and reproductive) are investigated, along with cytogenetic analyses. Certain rearrangements also provide excellent tools for investigations of homologous and nonhomologous synapsis and desynapsis, which are studied by electron-microscopic synaptonemal-complex analysis in spermatocytes. Mechanisms of chromosome pairing and segregation during meiosis play a major role in transmission of rearrangements. Finally, cytogenetic analyses of mutations can often provide information about the nature of lesions induced by specific mutagens. (RPIS 0184)

145. Protein Chemistry

F.C. Hartman

M.R. Harpel

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\$615,000

Enzymes serve as catalysts for biological processes; hence, studies of enzyme mechanisms are an integral part of acquiring an understanding of the myriad chemical reactions within living organisms. Such studies relate to adverse health effects of energy production because the clinical manifestations of concern—cancer, genetic damage, birth defects, acute toxic poisoning—represent perturbations of normal, enzyme-catalyzed cellular processes. The protein chemistry group focuses its efforts on characterization of active sites of enzymes by use of affinity labeling and site-directed mutagenesis. Identification of active-site residues and determination of their function bear directly on the elucidation of the principles underlying the two most unique properties of enzymes: their stringent specificity and their enormous catalytic efficiency. In addition to their value in the characterization of enzymic active sites, highly selective reagents offer a rational approach to the design of drugs, bactericides, fungicides, and pesticides. Enzymes of carbohydrate metabolism are under study. (RPIS 1472)

146. Protein Engineering and Molecular Mutagenesis

F.C. Hartman

S. Mitra

F.W. Larimer

S.K. Niyogi

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R.S. Foote

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\$1,080,000

Recombinant DNA technology permits custom tailoring of proteins by replacement, addition, or deletion of amino acids in targeted regions. Site-directed mutagenesis can elucidate functional roles of individual amino acid residues of a protein and should lead to improvement of biomedically and industrially important proteins. Project efforts focus on several functionally diverse proteins. One enzyme, ribulose biphosphate carboxylase/oxygenase, catalyzes the photosynthetic conversion of atmospheric CO₂ into carbohydrates. Oxygen, as both substrate and inhibitor of the enzyme, interferes with this process and can halve plant yield. These roles, as well as the feasibility of altering the ratio of the two activities, are investigated through substitution of active-site residues. Studies are also proceeding with human epidermal growth factor (EGF), a polypeptide that regulates cell growth. Properties of recently constructed EGF mutant proteins demonstrate the feasibility of designing both antagonists of EGF for potential cancer therapy and more potent growth factors. Recent success in the cloning and expression of human O⁶-methylguanine-DNA methyltransferase and N-methylpurine-DNA glycosylase, key proteins for alkylation damage repair, provides the opportunity to use site-directed mutagenesis to elucidate the regulatory mechanisms and structure-function relationships of these proteins. (RPIS 4463)

147. Theoretical and Applied Cryobiology

P. Mazur

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\$240,000

This program studies the responses of cells to freezing and thawing under conditions chosen to elucidate basic mechanisms of injury. Knowledge of these mechanisms is then used to devise methods for freezing cells and tissues of genetic, clinical, and agricultural interest. Often, basic knowledge and practical applications derive from the same series of experiments. Cells frozen to below -120° C will remain unchanged for 1,000 years or more. The utility of freezing to DOE's programs (especially genetics) stems from this stoppage of biological time. The chief use to date is the cost-efficient maintenance of mutant lines of mice in the form of frozen embryos. (The first successful freezing of mouse embryos was by this research group in 1972.) Low temperature banking not only prevents genetic drift, but it can provide a time-invariant yardstick against which to measure genetic drift in mutant lines maintained by standard procedures. The implications extend beyond mouse embryos. In agriculture, freezing and transferring of cattle embryos to surrogate cows is accelerating major genetic improvement in the productivity of cattle. Freezing

permits the storage of a wide variety of plant and animal germplasm that may be essential if, for example, new strains have to be developed in response to altered climatic conditions arising from use of fossil fuels. Current cells under study include mouse embryos, *Drosophila* embryos, human and bovine sperm, and human erythrocytes. (RPIS 0167)

148. Protein-Nucleic Acid Interactions

S.K. Niyogi

S. Mitra

A. Stevens

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\$360,000

An understanding of the molecular nature of protein-nucleic acid and protein-protein interactions as they pertain to the basic processes of growth, development, and differentiation is essential for exploring aberrations in the processes resulting from exposure to xenobiotic agents. This task explores several aspects of nucleic acid, protein metabolism, and modulation of expression of specific genes. Experimental approaches include human gene cloning, sequencing of specific genomic regions, and mutagenesis. Other approaches include enzymatic studies of DNA repair, regulation of transcription, messenger ribonucleic acid (mRNA) turnover, and action of growth factors. The regulation of two key enzymes responsible for repair of alkylation damage in DNA, namely O⁶-methylguanine-DNA methyltransferase and N-methylpurine-DNA N-glycosylase, is studied at the protein level and at the gene level. Modification of RNA polymerase by phosphorylation by tyrosine-specific protein kinases is studied to understand how such modification may regulate specific transcription. Turnover of mRNA is studied in an exoribonuclease mutant of yeast in which mRNA species accumulate. The interaction of the human epidermal growth factor with its specific cell surface receptor is investigated to understand the precise nature of growth factor signaling. (RPIS 0165)

149. Flow Cytometric Data Analysis

R.A. Popp

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\$110,000

Flow cytometric instrumentation has evolved to the point that most instruments can perform simultaneous measurements of five or more parameters per particle. Research on new fluorescent probes should make many more cellular features accessible to simultaneous measurement by flow cytometry (FCM). This project's flow cytometer is operated as a service and a research instrument. The research investigates methods of obtaining and analyzing multiparameter data generated by FCM. To exploit the potential of multiparameter FCM, it investigates methods for efficient processing and analysis of the large amount of data generated from these measurements. Most FCM sample sizes are virtually unlimited and preclude the use of certain standard methods of multivariate analysis due to prohibitively time-consuming calculations. The major problem is the optimal visualization and identification of subpopulations from multiparameter FCM data sets obtained

from heterogeneous cell populations. Visualization can be augmented through a combination of heuristics and artificial intelligence (expert system) software. These techniques combined with modified statistical methods are being pursued. Emphasis is on the detection and evaluation of changes in the incidence of subpopulations of cells that result from germinal mutations or are induced in somatic cells, through irradiation or chemical mutagenesis. (RPIS 4269)

150. Molecular Analysis of Mouse Mutations

E.M. Rinchik

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\$800,000

Germline (heritable) mutations of the mouse are useful and unique biological tools to augment genetic mapping analyses for regions of the mouse genome. They also provide experimental models for the identification and study of normal and abnormal developmental processes in mammals (including certain human abnormalities and diseases). This project focuses on molecular mapping of chromosomal regions associated with radiation- and chemical-induced (primarily multilocus-deletion) mutations that have been produced in mutation-rate experiments. These mapping strategies (carried on in collaboration with work proposal ERKP051) utilize techniques of transmission and developmental genetics and molecular biology, and emphasize two goals: (1) generating physical maps of DNA and (2) developing the important correlations between physical maps and genetic functional maps. Four chromosomal segments, comprising from 2-3 percent of the total mouse genome, serve as models for this intensive, regional, physical and functional mapping. Mapping of these segments provides basic data on the composition, structure, and biological function of regions of the mammalian genome, and also contributes to understanding the molecular mechanisms of mammalian germline mutagenesis. Moreover, molecular-genetic data obtained from these mouse model regions are being applied directly to the study of homologous regions of the human genome. (RPIS 4302)

151. Growth and Regeneration in a Land Crab Model System

D.M. Skinner

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\$250,000

Segments of repeated DNAs that adopt altered structures are often mutation hotspots. A satellite DNA (stDNA) of a land crab is a favorable model system because of its composition and complexity. Long, conserved domains are interspersed with hotspots containing tracts comprised of almost pure pyrimidines or purines—or alternating pyrimidines and purines—that assume unusual structures, including a Z-conformation. Studies on the crustacean molt cycle permit determinations of stDNA transcription in relation to growth. Four transcripts have been found in regenerating limbs. Also studied are molt-specific enzymes that degrade the old exoskeleton (a model for connective tissue degeneration) and proteins that comprise the new. Genes of these enzymes will be cloned. (RPIS 0158)

152. Insertional Mutagenesis and Gene Analysis*R.P. Woychik*

(615) 574-0865

\$775,000

The molecular analysis of mutations in mice is an effective way to establish a structure-function relationship between a complex phenotype in the animal and an individual gene on the genome. Insertional mutations in transgenic mice are particularly useful for this purpose because the mutant locus is "tagged" with a marker DNA fragment and can be readily cloned using standard procedures. To derive a large number of mutations which can be directly cloned and studied at the molecular level in the mouse, this project is conducting a large scale insertional mutagenesis program. Several new insertional mutations have been identified and are subjected to an indepth molecular analysis. In addition, probes derived from transgenic mice are used to analyze the molecular structure and expression of genes associated with agent-induced or spontaneous mutations. (RPIS 5185)

153. Carcinogen-Cell Genome Interaction*W.K. Yang*

(615) 574-0700

\$225,000

The purpose of this study is to elucidate the critical genetic mechanisms and specific cellular genes susceptible to alterations by environmental agents that ultimately lead to cancer formation. Experimental models of laboratory mice are used, including somatic transgenic mice and germline transgenic mouse lines developed in this laboratory. Retroviral vectors carrying (Kirsten) v-ras, produced by special packaging cell lines and retroviral vector constructs, can be used to incorporate this specific oncogene into liver cells in the animal by a special procedure. An accelerated kinetics of malignant hepatoma formation is observed in the treated C3H/Anf mice. Effects of environmental carcinogens, such as accumulation of injected radioactive plutonium in the liver, on further acceleration of hepatoma formation are assessed in this somatic onco-transgenic mouse model. Also, the researchers consider that different chromosomal retroviral gene classes are probably induced to initiate the retro-transposition mechanism by environmental carcinogens, thus causing genomic instability. Research aims are to characterize specific nuclear proteins that can interact with the regulatory cis-elements in the long terminal repeats of these chromosomal retroviral genes and to examine the ability of environmental carcinogens to affect those putative trans-acting factors of the cell. (RPIS 1701)

**Radiation and Chemical Effects:
Cellular and Molecular Biology**

*Offsite Grants***Associated Western Universities**

Salt Lake City, UT 84111

154. Cooperative Research Participation Program*D.I. Walker*

(801) 276-0799

\$50,000

Through this program, Associated Western Universities, Inc., provides opportunities for faculty and students from various colleges and universities to participate in energy-related research in the life sciences at DOE facilities and affiliated research centers throughout the U.S. Participants are selected competitively and are awarded grants and fellowships in support of research opportunities in the laboratories. Through the research experience, these participants gain access to the considerable resources of the DOE laboratories, including state-of-the-art instrumentation unavailable at many academic institutions. While enhancing the knowledge and broadening the perspectives of participants, the collaboration also infuses new ideas and enthusiasm into DOE research programs. (RPIS 8718)

University of California, Berkeley

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Division of Biochemistry and Molecular Biology**155. Endonucleases Involved in Repair and Recombination of DNA***S. Linn*

(415) 642-7583

\$100,000

The overall goal of this research is to understand the molecular basis of DNA damage and the mechanisms by which mammalian cells repair that damage. Most recently, investigators purified human DNA polymerase ϵ , showed it to be a unique and newly described enzyme, and adapted it to assay for other DNA repair factors. In this way, investigators partially purified factors for DNA repair that appear to be defective in persons with xeroderma pigmentosum, groups A and E. Investigators showed that an additional DNA repair factor, a finding protein specific for certain DNA lesions, is absent from two strains of xeroderma pigmentosum group E cells, but present and normal in many others. Investigators also purified and characterized ultraviolet endonuclease III, a correcting factor for xeroderma pigmentosum group D cells, and ultraviolet endonucleases I and II. Finally, investigators identified, purified, and characterized AP endonuclease and DNA glycosylase activities from mammalian mitochondria. Based on this work, it appears that mitochondria have the means to carry out base-excision DNA repair of oxidative damage.

In the current work, investigators are attempting to clone genes to study the mechanisms of the DNA binding protein noted above and of ultraviolet endonucleases I, II, and III. Investigators are studying the molecular biology and biochemistry associated with responses to DNA damage of the sort recognized by these factors, e.g., that caused by free radicals generated by radiation and various chemicals. (RPIS 10699)

University of California, Davis Davis, CA 95616

Genetics Department

156. Studies of the Repair of Radiation-Induced Genetic Damage in *Drosophila*

J.B. Boyd

(916) 652-8861

\$196,000

This analysis of eukaryotic DNA repair employs *Drosophila* as a model organism. This study began with the isolation and characterization of repair-deficient mutants in more than three dozen genes. Biophysical and biochemical approaches were then employed to identify a variety of DNA repair defects among these mutants. Investigators are currently employing recombinant DNA technology to pursue the mechanisms of the DNA repair pathways defined by those mutants.

Current cloning efforts are focused on the mei-41, mei-9, mus209, and mus308 genes required for postreplication repair, excision repair, cell cycle control, and DNA crosslink resistance, respectively. These genes serve as potential models for the variant and classical forms of xeroderma pigmentosum, as well as for Fanconi anemia in humans. The strategy employed to clone these genes is based on transposon tagging, coupled with chromosomal walking. Investigators have cloned the mei-41 gene in a chromosomal walk and are conducting chromosomal walks to recover the remaining three genes. Once investigators have cloned and characterized these major DNA repair genes, a variety of studies directed at understanding their functions and those of homologous genes in other organisms are initiated. A major effort is being devoted to the recovery of the homologous human genes.

This program also includes an investigation of the mechanism of DNA double-strand break repair. Investigators have recently demonstrated that the mei-41 and mus302 genes participate in that process. Detailed genetic and molecular analyses of these genes are contributing to an understanding of the essential repair process. (RPIS 9673)

University of California, Irvine Irvine, CA 92717

Department of Ecology and Evolutionary Biology

157. Genetic Variation in Resistance to Ionizing Radiation

F.J. Ayala

(714) 856-8293

\$99,000

The investigation addresses genetically determined individual differences in sensitivity to ionizing radiation. The model organism is *Drosophila melanogaster*. The gene coding for Cu,Zn superoxide dismutase (SOD) is the target locus, but the effects of variation in other components of the genome that modulate SOD levels are also taken into account.

SOD scavenges oxygen radicals generated during exposure to ionizing radiation. It has been shown to protect against ionizing radiation damage to DNA, viruses, bacteria, mammalian cells, whole mice, and *Drosophila*.

The role of SOD levels in radioresistance is investigated through a series of experiments that measure the somatic and germ line effects of increasing doses of ionizing radiation: (1) lethal-dose-50 of different genotypes after irradiation during the first larval instar and third larval instar; (2) genotype-dependent longevity effects of the irradiation; (3) sterility-dose-50; (4) genotype-dependent rate of lethal mutations in stage 7 oocytes, early spermatids, with oxygen enhancement, and catalase inhibition; (5) correlation between SOD levels (attributable to genetic differences other than the SOD locus) and sensitivity to irradiation; and (6) induction of SOD levels by irradiation. Additional experiments characterize molecularly the CA1 allele and the character, size, and rate of its transcripts.

The project has cloned a 2-kb region that comprises the SOD gene in *Chymomyza amoena* and *Ceratitis capitata* and is proceeding with the sequences. The divergence times between the species studied are 5, 30, 45, and 80 million years ago, which correspond to the divergence times between mammal lineages, for which the SOD amino acid sequence analysis shows a 5-fold increase of rate of evolution. Comparisons between the nucleotide sequences in diptera and mammals test whether the acceleration is distinctive of the mammals or, rather, reflects an overall acceleration of the SOD evolution on the Earth over the last 100 million years. These comparisons test the hypothesis of the molecular clock of evolution. (RPIS 9899)

University of California, Los Angeles
Laboratory of Biomedical and
Environmental Sciences
 Los Angeles, CA 90024

Division of Biomolecular and Cellular Sciences

158. DNA Replication, Recombination and Repair

J. Colicelli

(213) 825-9431

\$209,000

Efficient DNA repair and recombination are essential in all organisms. These pathways have been analyzed both genetically and biochemically in procaryotes, and they have been studied with some success in simple eucaryotes. This project uses yeast mutants defective in repair and recombination to isolate mammalian genes involved in these pathways. Functional complementation is used to isolate cDNAs which are analyzed first by sequencing to determine their primary structure and relatedness to known genes. A functional analysis of the gene products is carried out using genetic and, where possible, biochemical approaches. In addition, isolated genes are used as probes in the analysis of human diseases with underlying defects in repair and recombination. (RPIS 9232(A))

159. Biosynthetic Control

A.J. Fulco

(213) 825-8750

\$188,000

Current research exploits the discovery that barbiturates such as phenobarbital, which can function as tumor promoters in higher animals, act as potent nonsubstrate inducers of several unique cytochrome P450s in the bacterium, *Bacillus megaterium*. The major goal of this investigator is to perform a comprehensive analysis of the induction mechanism and molecular biology of this group of bacterial P450 monooxygenases and to apply this knowledge to the mechanism of barbiturate-mediated induction of the analogous P450 systems in mammalian liver. (RPIS 9805(A))

160. Hematopoietic Toxicology

E.F. Hays

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\$93,000

Malignant transformation of thymocytes in the mouse is the result of a stepwise process. This process produces a genetic change in a T cell progenitor in the thymus, which leads to blast transformation and a persistent replicative state. Viruses, chemicals, and irradiation are all genotoxic, and they all can produce this neoplastic transformation of thymocytes. Research in this project is directed to defining the changes in cellular interactions and gene expression caused by retroviruses, which result in thymic lymphomagenesis. (RPIS 9805(B))

161. Cell Biology and Gene Expression

H.R. Herschman

(213) 825-8735

\$193,000

Agents such as growth factors, hormones, morphogenetic agents, and neurotransmitters alter cell functions such as initiation of cell division and differentiation in the cells of multicellular organisms. They do so by regulating gene expression and thereby controlling the synthesis of proteins that determine cellular phenotypes. Xenobiotic agents such as heavy metals, carcinogens, tumor promoters, and radiation interdict these normal regulation processes of gene expression by endogenous factors. As a result, they often alter and derange normal biological processes following aberrant gene expression. This project studies (1) basic mechanisms of the regulation of gene expression by endogenous agents such as growth factors, hormones, and neurotransmitters; (2) altered regulation of genes by exogenous agents such as heavy metals and tumor promoters and the consequences of such alterations for cellular phenotype; and (3) causal steps in the induction of cell division in resting cells in response to mitogenic agents. (RPIS 9232(B))

162. DNA Damage and Gene Expression

K. McEntee

(213) 825-9431

\$91,000

The DNA damage responsive (DDR) genes of *Saccharomyces cerevisiae* respond to a variety of physical and chemical agents or treatments that damage DNA, disrupt chromosome structure, or perturb DNA replication. The DDR genes may constitute part of an SOS-like regulon in a eukaryote which controls mutagenesis, cell division, replication, and DNA repair activities. The research goals are to (1) identify the promoter elements that are necessary for transcription of the DDR genes; (2) identify by biochemical and molecular means transacting regulators that mediate stress-induced transcription of the DDR genes; (3) determine the functions of DDR genes in stressed cells as well as in unstressed cells; and (4) determine the components of the signal transduction pathway(s) which transmit the stress signal to the transcription apparatus. (RPIS 9805(C))

**University of California, Los Angeles
School of Medicine
Los Angeles, CA 20024**

Department of Pathology

**163. Genetic Localization of Ataxia Telangiectasia
Gene(s): A Human Gene(s) for Radiation
Sensitivity**

R.A. Gatti

(310) 825-7618

\$230,000

When the gene for Group A Ataxia Telangiectasia (AT) was first localized to chromosome 11q22-23, investigators observed that LOD scores were even higher when data from other AT families were included that had not been assigned to complementation Group A. This observation suggested that other complementation groups might also link to 11q22-23. Subsequently, investigators have shown that AT families assigned to Group C also link to genetic markers in this region. Researchers have also shown that the transfer of chromosomal fragments from 11q corrects the radiosensitivity of Group D fibroblasts. Together, Groups A, C, and D comprise more than 97 percent of tested AT families. Genetic linkage studies of more than 150 AT families (using a Monte Carlo simulation method of analysis) further localize the AT gene(s) to a region flanked by three proximal markers (STMY, S35, and CJ52.75) and by three distal markers (D11S132, NCAM, and CJ52.77). Within this region, a best supported confidence interval of 5.2 centimorgans (cM) (sex-averaged) can be conservatively estimated; in this region of the genome, this is equal to a 2.8 cM male-specific interval. Other efforts are underway to map additional markers in this region and to characterize candidate genes. (RPIS 9686)

**University of California, San Diego
San Diego, CA 92093**

Department of Pharmacology

**164. The Molecular Basis for Ultraviolet Response of
Cultured Human Cells**

M. Karin

(619) 534-0240

\$100,000

This project analyzes the mechanisms by which ultraviolet (UV) and another DNA damaging agent, H_2O_2 , increase the activity of transcription factor AP-1 in HeLa cells. Following UV irradiation of HeLa cells or treatment with H_2O_2 , the expression of *jun* genes, known regulators of AP-1, are determined. The project also investigates the common signal by which DNA damaging agents activate the UV response. The direct effects of DNA damage and of the induction of oxidative stress within the cell are compared for their effect on the induction of the UV response. Finally, the project is purifying and characterizing a factor, UVIC, that is secreted by UV-irradiated cells that protects non-irradiated cells from radiation damage. (RPIS 9515)

**University of Chicago
Chicago, IL 60637**

Department of Molecular Genetics and Cell Biology

**165. Factors Affecting Mutational Specificity Induced by
Ionizing Radiation and Oxidizing Radicals**

B. Strauss

(312) 702-8604

\$90,000

This project analyzes factors affecting the specificity of mutational change as induced by ionizing radiation and oxidizing radicals. The goal is to understand not only the rules that affect base substitution but also the mechanism(s) by which additions and deletions are produced, since deletions are a common consequence of radiation. Analyses are carried out in an in vitro mutation system that permits an analysis of base sequence, of polymerase, and of mutagenic agent. The system is designed to screen out most direct breaks as a cause of mutations and should indicate the changes resulting from base damage to DNA. Four specific questions are addressed. (1) What types of base substitution mutations are induced by ionizing radiation and oxidizing radicals? (2) Are deletions and/or additions produced? (3) Is there a difference in the type of mutation produced dependent on the polymerase used? Do mammalian polymerases plus their accessory factors result in different patterns of mutation? (4) What is the mechanism by which base damage is converted to mutation? This project utilizes an in vitro system in which mutations generated by the in vitro copying of a reporter gene sequence can be easily scored. (RPIS 9844)

**University of Chicago Medical Center
Chicago, IL 60637**

Joint Section of Hematology/Oncology

**166. Correlation of Chromosome Patterns in Leukemic
Cells of Patients with Exposure to Chemicals and/or
Radiation**

J.D. Rowley

(312) 702-9153

\$350,000

Patients with malignant diseases are treated with a wide variety of chemical agents, and often also with radiation, to cure their tumors. An unfortunate consequence of radiation is that 3-51 percent of the patients develop treatment-related acute myeloid leukemia (t-AML). The goal of this project is to identify both the common and the rare chromosome aberrations in the leukemic cells.

Among 129 t-AML patients, most had received alkylating agents, and 96 (75 percent) had loss of all or part of chromosomes 5 and/or 7. Recently, patients have been treated with epipodophyllotoxins or anthracyclines; many of these t-AML patients had balanced translocations, usually involving chromosome band 11q23 (seven patients) or 21q22 (five patients).

Investigators are cloning the breakpoint junctions of the t(9;11) and t(3;21). Investigators have identified a large cDNA at the 11q23 breakpoint that they call the myeloid/lymphoid leukemia (MLL) gene. Cloning and sequencing of the cDNA is in progress. Investigators are mapping the breakpoint variability of MLL in different patients with the same translocation.

The epipodophyllotoxins and the anthracyclines being used in treatment are topoisomerase II (topo II) inhibitors; they increase the frequency of chromosome breaks in cultured cells. Researchers are investigating whether there is an association between topo II inhibitors and specific chromosome abnormalities in t-AML. Investigators are also mapping the scaffold attachment regions (SAR) in the genes at the 11q23 and 21q22 breakpoints, because SARs often contain topo II binding sites. A functional alteration of topo II may be an integral component not only of balanced translocations in t-AML, but also of these same translocations in AML de novo. If this is the case, these studies provide critical insights into one mechanism of chromosome translocation in neoplastic cells. (RPIS 9474)

The Johns Hopkins University Baltimore, MD 21205

Department of Biochemistry

167. Role of DNA Damage and Repair in Chronic Disease

L. Grossman

(410) 955-3671

\$99,000

The overall goal of this project is to understand the mechanisms by which organisms monitor and repair damage to their genetic material. These researchers' model system for examining DNA repair is the *E. coli* *uvr* ABC system that catalyzes the incision of damaged DNA. The genes of this system have been cloned, mapped, sequenced, and amplified. The resulting reagent quantities of homogeneous UvrA, UvrB, and UvrC proteins allowed investigators to examine in detail the individual partial reactions leading to the dual incision stage of nucleotide excision repair.

The pre-incision steps can be subdivided into a number of partial reactions that include (1) UvrA dimerization, stimulated by ATP binding; (2) UvrA nucleoprotein formation at both damaged and undamaged sites; (3) the accompanying topological unwinding stimulated by ATP binding; (4) waves of supercoiling ahead of and behind the UvrA,B helicase; (5) the participation of the UvrB cryptic ATPase in the (UvrA)₂UvrB-catalyzed strand displacement reaction; and (6) dual incision catalyzed by the presence of UvrC. The incision mechanisms precede the multinucleoprotein complex, requiring coordinated excision reactions catalyzed by UvrD, DNA polymerase I, and polynucleotide ligase.

In the main task of this research project, investigators are associating the anatomy, or structure, of the *uvrA* and *uvrB* gene products with their catalytic and protein properties. The focal points and role of ATP in the individual processes are also being

addressed. The protein sequences, or domains, of interest include putative ATP binding regions and zinc finger regions. These sites are engineered by oligonucleotide-directed mutagenesis, deletion mutagenesis, and site-directed random mutagenesis. The expression of the mutated genes is followed in appropriate *E. coli* *uvrB* deletion mutants, the individual clones sequenced and over-expressed in suitable expression vectors, and the catalytic and protein properties of the mutant and "wild type" proteins examined for the enzymatic phenotypes in the respective pre- and postincision steps. (RPIS 9462)

The Johns Hopkins University School of Hygiene and Public Health Baltimore, MD 21205

Division of Biophysics

168. Genes and Gene Expression: Localization, Damage, and Control—A Multilevel and Interdisciplinary Study

P. Ts'o

S.A. Lesko

P.S. Miller

(410) 955-4392

\$415,000

Three projects are involved in this research. The first project is the study of gene locations (sequence-specific DNA) and chromosomes (specifically, the centromere) for their three-dimensional spatial relationship in the interphasal nucleus. This study uses a computer microscopic imaging system with the aid of nucleic acid probes and fluorescent antibodies. It is possible to locate a single gene in the interphasal chromosome, such as the integration sites of human papilloma virus DNA in chromosome 13. This approach allows a spatial three-dimensional mapping of genes located along an interphasal chromosome using the centromere as a reference point to that chromosome. The spatial relationship of the centromere of three chromosomes in the interphasal nuclei is also being studied. This project aims to establish the basic structure of nuclear topography based upon spatial relationships among genes and chromosomes.

The second project involves the generation, resolution, display, and analysis of DNA restriction fragments. The first task is to detect DNA rearrangement through comparative studies of two genomic DNAs. The current method can detect unknown changes of one or several DNA restriction fragments in a population of several thousand DNA fragments, the size of bacterial or yeast genome. The process of detecting unknown DNA rearrangement in the mammalian genome without the need of a probe is also progressing. The third project studies the use of oligonucleotide analogues to block the expression of genes either through masking mRNA to prevent translation or splicing or directly blocking the double-stranded DNA through a triplex formation. These analogues are nuclease-resistant, nonionic, and penetrable into cells and tissues in humans and animals. Through this study, drug development can be made based on specific gene expression. (RPIS 9792)

Louisiana State University
Baton Rouge, LA 70803**Department of Zoology and Physiology**

- 169. Mutagenic Effects of Tritium on DNA of *Drosophila melanogaster***
W.R. Lee
(504) 388-1754 \$85,000

The overall goal of this research is to integrate molecular analysis of mutations with classical genetic analysis to better understand the process of mutation induction. Recent accomplishments with the sex-linked recessive lethal test in *Drosophila melanogaster* found a linear dose-response curve below 30 Gy for beta (β) radiation from a ^3H source and gamma (γ) radiation from a ^{60}Co source and the previously reported results of another researcher with 250 kVp x rays. The relative biological effectiveness (RBE) of the beta (β) particles was 2.7 times that of the γ radiation and 2.1 times that of 250 kVp x rays.

An explanation of the difference in RBE between different sources of ionizing radiation requires a detailed molecular and genetic analysis. For analysis at the molecular level, investigators recovered 23 mutations induced by β radiation at the alcohol dehydrogenase (*Adh*) locus in *D. melanogaster*. All 23 ^3H -induced *Adh*^a were multilocus deletions when tested by complementation tests and Southern blots. In contrast, 9 of 28 x ray induced mutations at the *Adh* locus were intragenic mutations. Investigators sequenced these intragenic mutations and found that one was a single base transversion, five were intragenic deletions, one was a complex insertion, one was the result of recombination with the alternate null-allele, and one was lost. An important observation was that all of the deletions had a direct repeat at the breakpoint, with one of the repeats deleted.

Currently, researchers are inducing a comparable set of mutations for the low linear energy transfer (LET) ^{60}Co (γ) radiation and mapping the breakpoints of the multilocus deletions using complementation mapping, Southern blots, cloning, and sequencing the region of the breakpoint. This work compares the molecular level of high LET ^3H (β) radiation with both 250 kVp x ray and ^{60}Co (γ) radiation. The unique characteristics being observed are valuable as biomarkers in the molecular analysis of mutations observed in humans. (RPIS 9460)

Massachusetts Institute of Technology
Cambridge, MA 02139**Center for Environmental Health Sciences**

- 170. Mutagenesis of Human Cells In Vivo and In Vitro**
W. G. Thilly
(617) 253-3258 \$364,000

The goal of this research is to discover the causes of mutation in humans. Investigators hypothesize that primary causes of mutation exist in human tissues and that these causes may be discovered by obtaining the point mutational spectrum from tissue cell samples. To obtain mutational spectra from human cells, investigators have developed a new technology based on a combination of (1) denaturing gradient gel electrophoresis to separate mutant from nonmutant DNA sequences and (2) high fidelity DNA amplification to permit detection, enumeration and sequence determination of the most prominent events (hot spots) in a mutational spectrum. The technology has developed so that all point mutations appearing as hot spots may be detected and enumerated in any selectable gene sequence. To build a reasonable database for different chemical mutagens and radiation mutagens, researchers have examined the spectra of some 7 mutagens in a human B cell X-linked gene (*hprt*, exon 3) and are examining 10 more. Present uses of mutational spectrometry include basic studies of human cell mutation pathways and discovery of the primary mutagens in complex environmental mixtures. Investigators are determining or have already obtained spectra for radiation- and chemical-induced and spontaneous mutations. More important, however, are the developments aimed at permitting direct study of mutational spectra in human tissues. Already investigators have discovered a set of mutations with four separate 100 bp mitochondrial sequences that are remarkably similar among cells obtained from four healthy adults of European, African, and Asian ancestry. Whether these are common hot spot mutations arising in somatic cells or common mutations arising in the course of maternal germ cell development is not yet clear. To study mutational spectra in single copy genes of interest such as onco- or suppressor genes—investigators are working on two fronts: increased separation power by means of a capillary gel electrophoresis variation of denaturing gradient gels and increased fidelity of polymerase chain reaction using antimutator T4 DNA polymerase with accessory proteins. (RPIS 9536)

**Michigan State University College of
Osteopathic Medicine**
East Lansing, MI 48824

Carcinogenesis Laboratory

**171. Malignant Transformation of Diploid Human
Fibroblasts by Transfection of Oncogenes**

J.J. McCormick

(517) 353-7785

\$200,000

To understand why human fibroblasts are refractory to carcinogen-induced malignant transformation these researchers have transfected them with oncogenes active in transformed rodent fibroblasts or human tumorigenic fibroblasts derived from fibrosarcomas. Research shows that active H- or N-*ras* genes flanked by suitable enhancer and promoter sequences are able to cause normal human fibroblasts to express many transformed phenotypes. However, such cells senesced after the expected in vitro lifespan and did not form tumors in athymic mice. When H-, or N-*ras* genes (in the same constructions used above) or the v-K-*ras* gene are transfected into MSU 1.1 cells—an infinite lifespan, near diploid nontumorigenic cell strain developed in this laboratory—foci form. Cells from these foci formed progressively growing, invasive fibroblastic tumors in athymic mice. The premalignant, as well as the tumor-derived cells, transfected with the H- and N-*ras* gene overexpress the p21 *ras* protein. The p21 viral K-*ras* p21 *ras* protein was not overexpressed. The H-*ras* gene in the same construction used above causes malignant transformation of two other infinite lifespan human fibroblast lines, the KMST-6 cells of Namba and GM637 cells, which was transformed with SV40. This suggests that the infinite lifespan phenotype is required for malignant transformation.

Because the oncogenes used in these studies are homologous to the human proto-oncogenes, this research project intends to replace transfection of such oncogenes with carcinogen-induced activation of the proto-oncogene as the appropriate selection techniques are understood. This method should lead to a quantitative, mechanistic understanding of malignant transformation. (RPIS 9645)

**National Institute of Standards and
Technology**

Gaithersburg, MD 20899

Ionizing Radiation Division

**172. Ionizing Radiation-Induced DNA Damage and Its
Repair in Human Cells**

M.M. Dizdaroglu

(301) 975-2581

\$100,000

The objective of this research project is to understand ionizing radiation-induced damage to chromatin DNA in human cells, its cellular repair and biological consequences. Radiation-

induced damage to cellular chromatin DNA being studied includes base damage, DNA-protein crosslinks, and sugar damage.

An understanding of these types of DNA damage in living cells requires their chemical characterization and quantification. Methodologies involving the GC/MS technique have been developed in the National Institute of Standards and Technology laboratory in recent years to measure various lesions in chromatin DNA. They permit measurement of modified DNA bases directly in chromatin without first isolating the DNA from chromatin.

Recent accomplishments involve measuring a large number of modified bases in DNA of isolated chromatin under various gaseous conditions (argon, air, N₂O, N₂O/O₂) that provide different radical environments in irradiated systems. Additionally, DNA base modifications chromatin by metal ions and hydrogen peroxide were identified and quantitated. A number of DNA-protein crosslinks in irradiated chromatin was characterized, and the effect of oxygen on their formation was studied. Modified bases in chromatin DNA of irradiated cultured human cells were also identified and quantitated.

Current objectives include the measurement of DNA-protein crosslinks in chromatin of irradiated cultured human cells and the study of cellular repair of the base lesions and DNA-protein crosslinks identified. (RPIS 10059)

New York University

New York, NY 10003

Biology Department

**173. Molecular Understanding of Mutagenicity Using
Potential Energy Methods**

S. Broyde

(212) 998-8231

\$54,000

Polycyclic aromatic amines and hydrocarbons include mutagenic and tumorigenic substances that are widespread in the environment as a result of fossil fuel combustion and other causes. The initial event in mutagenesis and tumorigenesis can originate from DNA damage by binding these substances to the genomic material. The resulting lesion may alter the DNA conformation so that replication is not faithful, or so that repair fails or is error-prone and thus causes a mutation. The investigators' goals are to understand the conformational effects of the damage by mutagenic and tumorigenic substances and to compare such malignant moieties with benign ones and with unmodified DNA. Investigators employ minimized potential energy calculations with the program DUPLEX and molecular dynamics calculations with AMBER to obtain static and dynamic atomic resolution views of the DNAs, both modified and unmodified. Experimental information obtained by collaborators with nuclear magnetic resonance (NMR) methods is included in the calculations when available. Novel strategies for searching conformation space are being developed in this effort. The particular substances being explored in

depth include aniline (AN), 2-aminofluorene (AF), 2-acetylaminofluorene (AAF), and benzo[a]pyrene-diol-epoxide (BPDE) adducts to DNA. Molecular views of AF and AAF adducts in solution that include experimental NMR data have recently been achieved. Studies including NMR data on BPDE adducts are being planned as are investigations of effects of varying base sequences surrounding the lesions on conformation. An understanding of the conformational effects of mutagenic substances and of benign analogues is expected to permit prediction of mutagenic potential by computational methodologies. (RPIS 10180)

Chemistry Department

174. Base Sequence Effects on Interactions Between Aromatic Mutagens and DNA

N.E. Geacintov

(212) 998-8704

\$100,000

The mutagenic potentials of the various stereo-isomeric polycyclic aromatic hydrocarbon diol epoxides (PAHDE) are believed to depend on (1) the formation of covalent adducts with DNA bases (mostly with guanines and adenines), (2) adduct stereochemistry (cis versus trans addition), (3) the conformation of the PAHDE-DNA lesion, and (4) the sequence of bases in which this lesion is located. The objectives of this research are to determine how the sequence of bases on the 3' and 5' sides flanking the target nucleic acid base affect (1) the binding of different PAHDE stereo-isomers to this target base and (2) the conformational and other physical properties of the bound mutagen.

The basic approach consists of synthesizing site-specific, stereochemically defined PAHDE adducts with monomeric, dimeric, trimeric, and higher deoxyribonucleotides of defined base composition and sequence. Fluorescence, ultraviolet absorption, circular dichroism, thermodynamic, and nuclear magnetic resonance techniques are employed to characterize the effects of the bulky lesions on their interactions with neighboring bases in the single-stranded forms and in complexes with the complementary strands. Recent results obtained with 5'-d(GC) and 5'-d(CC) and related di- and trinucleotides with single dGs (the preferred target base of benzo[a]pyrene-7,8 diol-9,10-epoxide, or BPDE) suggest that different stereoisomers of BPDE form adducts with different orientations relative to the 5'→3' polarity of the modified strand. Such differences in adduct orientations may account for the differences in the biological activities of various BPDE stereoisomers. (RPIS 9840)

University of Rochester School of Medicine Rochester, NY 14642

Department of Biophysics

175. Molecular Mechanisms of Mismatch Repair Mutagenesis

C.W. Lawrence

(716) 275-2948

\$100,000

The long-term aim of this research is to understand the molecular mechanisms that lead to the production of mutations in mutagen treated cells. Single-stranded vectors are being constructed that carry a uniquely located and defined mutagenic photoproduct. Double-stranded vectors, carrying a lesion in each strand, are also being made. Following the replication of these vectors in yeast, the molecules are sequenced at and around the site of the photoproduct to determine the frequency and type of mutations produced. The properties of different lesions (cyclobutane dimers, 6,4 pyrimidine pyrimidone dimers, abasic sites) are determined as well as the effect of flanking nucleotides and ultraviolet-irradiation to the cells. Different mutant strains of *Saccharomyces cerevisiae* are used (rad6, rev1, rev3, rev6, rev7, ngm2, rad18, rad9, etc.) to define the genes required for translesion synthesis. This research provides insights into the reasons why mutagenic lesions are mutagenic, the ways lesions can be bypassed, and the conditions for bypass. (RPIS 9782)

176. Excision Repair of Ultra-Violet Damaged DNA: Genes and Proteins of Yeast and Humans

L. Prakash

(716) 275-2656

\$324,000

The RAD1, RAD3, and RAD10 genes of the yeast *Saccharomyces cerevisiae* are required for the incision step of excision repair of ultraviolet (UV) damaged DNA. In addition, RAD3 is essential for cell viability, while RAD1 and RAD10 function in mitotic recombination. The objectives of this research are to perform genetic and biochemical studies with the RAD1, RAD3, and RAD10 genes and their encoded proteins, and with the human ERCC2 gene and protein, which shows a high degree of homology to the yeast RAD3 protein. To determine the essential role of RAD3, macromolecular synthesis and the cell cycle arrest stage are being examined at the restrictive temperature in rad3 ts mutant. RAD3 protein is being characterized for DNA:RNA helicase, binding to UV damaged DNA and to ARS sequences, and for stimulation of strand displacement synthesis by yeast DNA polymerases. Human ERCC2 protein is being purified and characterized for ATPase and DNA helicase activities. Purified RAD1 and RAD10 proteins are being examined for biochemical activities related to their role in excision repair and recombination. The studies should help elucidate the role of RAD1, RAD3, and RAD10 in excision repair and other cellular processes and provide information on the extent of functional conservation between RAD3 and ERCC2 proteins. (RPIS 9783)

University of South Carolina Columbia, SC 29208

Department of Biological Sciences

177. Characterization of Mammalian DNA Polymerase Gene(s) and Protein(s)

N.C. Mishra

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\$140,000

The long-term goal this research is to understand the nature of the key enzymes involved in eukaryotic DNA transactions. Investigators have purified and characterized at least three DNA polymerases from the Chinese hamster ovary (CHO) cell line K1 in order to evaluate the roles of different polymerases in eukaryotic DNA replication: pol α , pol δ , and pol ϵ . Pol α was the most abundant among different polymerases activities; it was neutralized by a monoclonal antibody raised against human pol α . Pol ϵ was separated from pol α and pol δ activities using DEAE Sephacell, phosphocellulose, and hydroxylapatite columns. The enzyme proved to be sensitive to aphidicolin and carbonyldiphosphonate and was not stimulated by PCNA. Pol δ was the least abundant among the three enzymes. It was sensitive to aphidicolin and carbonyldiphosphonate and was stimulated by PCNA. It had a preference for template/primer poly (dA-dT).

Based on DNA sequence data of different eukaryotic polymerases, polymerase chain reaction (PCR) primers complementary to two neighboring conserved regions were synthesized. In PCR experiments—using CHO DNA as template—several PCR products were obtained that are assumed to be specific for the CHO polymerases.

Investigators have also analyzed a large number of aphidicolin-resistant mutants of CHO to identify mutants with altered DNA polymerases. Some of these mutants possessed different specific activity of the enzymes and possessed a drug-resistance phenotype in *in vitro* assay. These mutants also showed restriction fragment length polymorphism for the DNA polymerase gene. Also, pulse chase analyses of DNA synthesis in the wild-type and mutant cell lines showed that the presence of aphidicolin inhibited the incorporation of Okazaki fragments into the larger DNA segment in the wild-type, but not in the mutant cell line.

Future studies will include the characterization of DNA polymerases, particularly DNA polymerases δ and ϵ and cloning of these genes. (RPIS 10318)

University of Washington Seattle, WA

Department of Biological Structure

178. Modulation of Lymphopoiesis

C. Rosse

(206) 543-4043

\$251,000

This project systematically analyzes the nature of molecular interactions between thymic epithelial cells and developing T lymphocytes in discrete anatomical regions of the thymic environment and generates the appropriate reagents that permit selection and *in vitro* propagation of the appropriate cell types. Three classes of molecules and their ligands have been selected for characterization and functional assessment with respect to their role in T lymphopoiesis: cell adhesion molecules, particularly integrins, novel stromal cell molecules that have been identified that appear to participate in T lymphopoiesis, and lymphocyte cell surface molecules that mediate adhesion. These experiments are a prerequisite for establishing a stromal environment that will support the development of appropriate T cell progenitors in a system that will permit the analysis of the factors that regulate T lymphopoiesis. This approach in developing a long term culture system for T lymphopoiesis will provide information on the receptor ligand interactions between stromal cells and progenitor cells on which T cell development relies. (RPIS 9475)

Radiation and Chemical Effects: Physical and Chemical Processes

Intramural DOE Laboratories

Argonne National Laboratory Argonne, IL 60439

Environmental Research Division

179. Molecular Radiation Physics

M. Inokuti

(708) 972-4186

\$485,000

The interaction of ionizing radiation with matter generates many reactive species (often called initial products), which start a chain of chemical reactions. These reactions eventually lead to net radiation effects that include biological changes. This work aims to establish the probabilities and mechanisms of the formation of the initial products. The resulting knowledge is used to model the physical stages of radiation actions; such modeling is an essential basis for radiation chemistry and

biology. The topics selected for study are timely ones and ones that can best be treated. Efforts are now primarily directed to theoretical studies on the following topics: (1) generalized oscillator strength of molecules, (2) electron collision cross sections, (3) kinetics of electron degradation and the yields of resulting products, (4) stopping powers and other radiological and dosimetric quantities, and (5) the mobility of electrons in condensed phases. To supplement theoretical studies, selected experiments are conducted on electron collisions. Recent measurements concern (1) energy deposition and fragmentation in DNA bases and related molecules and (2) cross sections for vibrational excitation, elastic scattering, and momentum transfer in polyatomic molecules. Extensive data thus generated are useful in modeling radiation effects. Some studies are also relevant to combustion chemistry and atmospheric chemistry, and provide basic data needed to evaluate health effects of nonnuclear energy technologies. (RPIS 0701)

Lawrence Berkeley Laboratory Berkeley, CA 94720

Cell and Molecular Biology Division

180. Radiological Physics and Chemistry: Mechanistic Theoretical Models for Radiation-Induced Mutation and Transformation

A. Chatterjee

(510) 486-5415

\$380,000

Several types of damages can be inflicted on DNA by ionizing radiation. DNA contains the important genetic codes; hence, its damage can have serious health consequences. In this project, the long-term goal is to correlate the physical and chemical changes that precede any specific type of damage to DNA with observable biological consequences to a cell. Ionizing radiation can cause strand breaks (single and double), base alterations, released bases, DNA-protein crosslinks, DNA-DNA crosslinks, etc. The short-term goal of this project is to correlate double strand breaks with mutation (specific types) and transformation frequencies as a function of dose for different qualities of ionizing radiation. The types of ionizing radiation being considered are x rays, Co^{60} -g rays, energetic protons, helium, and other heavy charged particles. Each of these radiation qualities has a characteristic physical pattern of energy deposition (track structure) that is primarily responsible for chemical changes, which can sometimes be qualitatively and quantitatively different. In addition, the proximity of various types of damages (which is a function of radiation quality) on DNA may have a strong influence on the observable biological effects. In the last several years, these researchers have developed a mechanistic theoretical model based on basic physical and chemical laws that can quantitatively estimate yields of strand breaks (single and double), base alterations by water radicals, and base deletions for any quality of ionizing radiation. Now the approach is to use the yields of strand breaks as fundamental quantities in modeling mutation and transformation frequencies.

For mutation studies, the researchers are limiting themselves for the next milestone to those cases where a foreign gene transfected into a host genome is deleted as a result of two double-strand breaks. Modeling of transformation effects is being initiated using available experimental data on partially transformed cell lines such as C3H10T1/2 and NIH3T3. The question being asked is the following: Is it true that a minimum of two proto-oncogenes must be activated for radiation-induced neoplastic cell transformation? To answer this question, researchers hypothesize that for partially transformed cell lines, only one proto-oncogenes must undergo activation. Hence, in the model researchers must estimate the probability of activation of one proto-oncogene through one of the following mechanisms: (1) point mutation of a proto-oncogene, (2) deletion of a suppressor gene by a single track, or (3) deletion of a suppressor gene by two particle tracks. Researchers will consider that all single strand breaks and some double strand breaks are repaired. The model, if successful, may be useful for evaluating risks at the lowest possible radiation dose for initiation of carcinogenesis. (RPIS 0705)

Los Alamos National Laboratory Los Alamos, NM 87545

Life Sciences Division

181. Radiobiology of Ultrasoft X Rays

M.R. Raju

(505) 667-2780

\$250,000

Ultrasoft x rays provide a unique tool for studying the physical parameters involved in biological damage by ionizing radiation because these x rays produce electrons with ranges similar to the sizes of critical structures in cells, such as DNA strands and DNA-histone complexes. The overall objective of the studies is to investigate, using ultrasoft x rays, the mechanisms by which ionizing radiation causes lesions in mammalian cells. The studies use the characteristic x-ray sources at Los Alamos, ranging in energy from 0.28 to 8.0 keV. In addition, the researchers study the energy dependence of biological effects using x rays from the National Synchrotron Light Source at Brookhaven, which allows continuous selection of x-ray energy. The Los Alamos beam line at Brookhaven is modified to accommodate this study. For all studies, accurate cell thickness measurements are made using optical plus electron and confocal microscopy to determine the absorbed dose within the cell nucleus for these severely attenuated x rays. Computer simulations of the energy deposition process are correlated with experimental results to extract information about critical parameters such as target site size and energy deposition range. These studies are helping to focus the radiobiology programs at synchrotron light sources. (RPIS 4591)

Oak Ridge National Laboratory
Oak Ridge, TN 27831**Health and Safety Research Division****182. Physics of Solids and Macromolecules***E.T. Arakawa**T.A. Callcott**I. Sauers**(615) 574-6218***\$173,000**

The program objectives are to understand and predict effects of pollutants on humans and their environment. Areas of research include (1) measurement, by a variety of techniques, of the optical properties of solids, macromolecules, liquids, and thin films over wide ranges of photon energies and temperatures; (2) resonance ionization mass spectroscopy; (3) surface-enhanced Raman spectroscopy; (4) soft x-ray emission spectroscopy; (5) photoacoustical measurements; and (6) measurement and calculation of low energy electron mean free paths in solids and macromolecules. Studies in this program should lead to a better understanding of biologically interesting materials and biological systems and to the development of new low level pollutant detectors. Basic observations also have direct application to understanding, predicting, and possibly modifying the behavior of selected systems, such as high temperature superconductors, thin film coatings for optical components, soft x-ray optical components and instruments, dilute metal alloys, multilayer systems, clusters imbedded in various solid matrices, and selected elements in organic materials. (RPIS 0721)

183. Chemical Kinetics of Irradiated Materials*C.H. Chen**W.R. Garrett**J.C. Miller**(615) 574-5895***\$163,000**

These studies are directed toward the production, spectroscopic characterization, transport, and chemical kinetic behavior of laser-induced transient molecular species such as free radicals, excited molecules, and molecular ions. Efforts focus on the development of new techniques that will permit such studies in the condensed phase and on thin film surfaces. The program emphasizes the kinetics of multiphoton processes for environmental and biological applications. This work should eventually lead to detailed understanding of kinetics for the radiation effect on the environment and on biology. (RPIS 1610)

184. Atomic, Molecular, and Interphase Physics*L.G. Christophorou**(615) 574-6199***\$134,000**

This program is devoted to quantitative studies aiming at linking knowledge of fundamental physical processes in gases with understanding of those in the condensed (mostly liquid) phase. The principal processes studied include photoionization, electron impact ionization, electron attachment and detachment, and electron and ion drift in dilute and dense gases (quasi-liquids) and in liquids. The evolution of the energetics of these processes with increasing gas density and the changes in their respective cross sections and rate constants are followed all the way from the dilute gas through the high density gas to the condensed phase. New equipment has been constructed to study the photoionization process as a function of density and to measure absolute electron impact ionization coefficients in very dense media over a wide range of densities. With tunable dye lasers and special experimental equipment constructed, researchers can also study the photodetachment process for ions in the liquid phase and compare its energetics with gas phase data. Laser and electron-molecule interaction studies are used to microprobe the liquid state of matter, to attempt to understand radiobiological mechanisms and effects, and to trigger new technological innovations involving the liquid and cryogenic state of matter. The possibility of developing superfast and supersensitive warm liquids for radiation detectors is also explored. (RPIS 0722)

185. Electron-Molecule Interactions*L.G. Christophorou**J.G. Carter**(615) 574-6199***\$219,000**

The object of this research is to determine the basic physical and chemical properties of molecules, especially chemical pollutants and toxic compounds, and to relate this knowledge to their interaction mechanisms. The program employs photophysical, laser, ion impact, and mass spectrometric techniques, as well as theoretical and computational methods. The main thrust of this study is to use a multiplicity of methods employing slow electrons. Earlier studies concentrated principally on the interactions of slow electrons with molecules of environmental and radiobiological interest, which are predominantly in their ground (lowest) state of excitation. This research is establishing a new and more difficult area: the interaction of electrons with energy-rich (excited) molecules, mostly environmental halocarbons and perfluorocarbons of radiobiological significance. Program efforts concentrate on the following three areas: (1) electron "hot" (vibrationally/rotationally) excited molecule interactions, (2) electron-electronically excited molecule interactions, and (3) transport properties of energy-rich molecules. These three areas are of both fundamental and applied significance. Most biological reactions involve excited molecules, and the interactions of the latter with electrons can be orders-of-magnitude larger compared with those of unexcited molecules. The same studies are crucial to the development of new radiobiological instrumentation (especially radiation detection devices) and new energy technologies. (RPIS 1603)

186. Chemical Physics Studies in the Gaseous and Liquid Phases

R.N. Compton
C.E. Klotz
H.S. Carman, Jr.
J.C. Miller
 (615) 574-6233

\$200,000

This program is devoted to mission-oriented basic research on the interaction of charge particles and photons with matter in the gaseous and liquid phase. The primary objective of this program is to examine the physical mechanisms through which charged particles and photons excite and ionize atoms and molecules in the gaseous and liquid phases. A central theme has been the detailed study of ionizing radiation in matter and the development of new methods for dosimetry applications. A major component of this program, which has been at the forefront of developing new and innovative laser applications technologies, concerns studies of multiphoton ionization of atoms and molecules using high-power tunable dye lasers. Multiphoton ionization photoelectron spectroscopy, for example, is a new and growing field that originated with this program. In addition, this program was one of the first to introduce resonance ionization mass spectroscopy. New research areas will involve the study of collisions of electrons and ions with laser-excited molecules. The use of polarized lasers (linear and circular) is expected to provide information on the interesting question of optical activity, especially with respect to optically active biomolecules. Basic knowledge and new technologies developed in these studies are directly relevant to health, environmental, and technological issues in atmospheric chemistry, pollutant detection, analytical chemistry, and isotope separation. This program also provides basic spectroscopic information on pollutant molecules, which can ultimately lead to the development of new and more sensitive and specific detection methodology. (RPIS 0719)

187. Liquid and Submicron Physics

T.L. Ferrell
R.J. Warmack
 (615) 574-6214

\$200,000

The basic objectives of this research are (1) microscopic determination of size, shape, and composition effects on optical properties and field amplification for submicron structures; (2) understanding of particulate-particulate and particulate-surface interactions; and (3) development of microscopic surface probes for liquids and solids, particularly those that use the photon scanning-tunneling microscope invented in this program. Allied research is performed in scanning electron microscopy, microlithography, radiation dosimetry, surface plasmon physics, Raman and Mie scattering, spectra of metal-insulator-metal tunnel junctions, electron scattering, and photoemission. In addition to fulfilling its research mission, the program involves several scientists from universities and industry and provides graduate funding. (RPIS 0720)

188. Microdosimetry, Biological Modeling, and Theoretical Biophysics

R.N. Hamm
J.E. Turner
R.H. Ritchie
 (615) 574-6207

\$145,000

The object of this project is to improve understanding of the physical and chemical interactions that radiation undergoes with biological material and to identify mechanisms or processes most significant in producing biological effects. These researchers are constructing basic cross sections for the initial physical events that occur when radiation interacts with matter. These cross sections are used to develop computer codes for transporting various types of radiation through biological material. Models are developed to link early physical events to later chemical events and ultimately to biological effects. The project will result in a better understanding of the following: (1) the initial processes by which radiation interacts with matter, (2) the structure of charged-particle tracks in biological materials, (3) the mechanisms by which energy is transported through matter, (4) the physical and chemical changes that follow irradiation, (5) the processes or mechanisms that are most significant in producing biological effects, and (6) the improvement of models for predicting biological response to radiation. (RPIS 1706)

189. Ion Chemistry and Molecular Clustering Phenomena

C.E. Klotz
R.N. Compton
H.S. Carman, Jr.
J.C. Miller
 (615) 574-6234

\$398,000

This task is concerned with the modification of the properties of isolated molecules upon introduction into the condensed phases and with the resultant new phenomena which may have little significance at the molecular level. The program is specifically designed to adapt the understanding of isolated molecules to more complex environments, such as the urban atmosphere, or to condensed phases, and in particular, to matter subjected to high energy radiation. Sonic nozzle expansions, laser ablation time-of-flight mass spectroscopy, and photoelectron spectroscopy are used. One component of this program involves studies of laser ablation of large (biological) molecules and clusters of molecules into the gas phase using the picosecond laser facility in the chemical physics section. New areas of research will involve laser photo-ion microscopy and laser-enhanced surface ionization of biomolecules. Studies of the interactions of these molecular aggregates with electrons, photons, and molecular beams provide detailed information on their stability and reactivity. Recent reports of the discharge method of producing gram quantities of the so-called Buckeyball (C60) structures have prompted further studies in this area at Oak Ridge National Laboratory (ORNL). An apparatus has been assembled to generate sufficient quantities (C60) to be used in studies in this

group as well as others at ORNL. Unique facilities are capable of a distinct number of experiments, which will further characterize the interesting properties of C60 (e.g., ionization potential, electron affinity, band distances, etc.). (RPIS 4833)

190. Transport and Surface Physics

R.H. Ritchie

(615) 574-6208

\$228,000

The objective of this project is to understand the basic physical interactions of radiation with matter and the fundamental processes by which humans are affected by nuclear radiation. The concepts and methodologies developed in this program have application in a variety of areas of basic physics and chemistry, such as integrated optics, electronic device phenomena, superconductivity, catalysis, and aerosol physics. This work is relevant to the elucidation of problems arising in studies of energy utilization, conversion, and production. It represents a long-standing, broad, integrated approach to the understanding of radiation effects in condensed matter. The goal is to relate the physical and chemical properties of biological systems to their response to corpuscular radiation. Mathematical models that incorporate essential properties such as collective electronic and ionic oscillatory motion in the condensed phase are actualized using basic analytical techniques of physics supplemented by computer studies. This work is closely coupled with experimental programs directed toward the stated goal and complements them, interpreting and suggesting new experiments. (RPIS 0718)

Pacific Northwest Laboratory

Richland, WA 99352

Life Sciences Center

191. Radiation Dosimetry

L.A. Braby

(509) 376-5916

\$330,000

To minimize the risks of adverse health effects from energy production and conservation, researchers must be able to predict the consequences of changes in the radiation and chemical environment. Because the exposures of concern are those that produce only marginal risk of biological effects, it is impractical to characterize the risks of direct observations of experimental populations. Instead, researchers must understand the mechanisms that lead to the effects of concern and then develop quantitative models describing those mechanisms as they apply to different radiations and exposure conditions. The basis of such models must be an accurate and relevant description of the interaction of the radiation with the biological system. However, the fact that equal doses of different radiations—differing only in the spatial and temporal distribution of the initial interaction products—can result in dramatically different biological effects indicates that average energy deposited is not an adequate description of the physical process that initiates the biological changes. The physical

characteristics of the energy deposition apparently interact with the biological processes that modify radiation damage. Thus, it is necessary to understand the biological processes to produce a suitable description of the radiation interactions. This project develops and tests mathematical models of radiation response processes and of the distribution of radiation interactions. A realistic characterization of these processes, when completed, provides the means to accurately predict the effects of different radiations and the interactions between radiations and other environmental hazards. (RPIS 0738)

192. Radiation Physics

R.D. DuBois

(509) 376-2305

\$600,000

The primary objective of this project is to develop a quantitative understanding of the fundamental processes of energy deposition and energy transport following the interaction of high linear energy transfer (LET) radiation with biologically relevant material. Information obtained from this study contributes directly to the knowledge of the spatial and temporal distributions of energy deposited by high LET radiation, determining factors in the ultimate expression of biological damage. Experimental and theoretical studies of differential cross sections for energy loss by charged particles, with emphasis on those representative of neutron-induced recoils in tissue and radon alpha particles, are conducted to provide quantitative information and insight into the energy deposition process. Mathematical models of energy degradation and transport are developed using these data to describe the initial pattern of energy deposition in representative biological media. Emphasis is on understanding the role of the heterogeneous nature of the cellular environment in the energy transport process. Recent studies focus on differential cross sections for ionization by ions that possess bound electrons and on understanding the reaction channels leading to electron production by fast charged particles. These experimental studies are complemented by Monte Carlo-based energy transport studies that focus on understanding the systematics of local energy deposition in molecular and cellular systems. Knowledge of energy deposition processes and models of energy transport contribute to the ability to extrapolate observed biological effects as a function of dose, dose rate, and radiation quality. This capability is vital to obtaining reliable estimates of potential health effects of radiation exposure at environmental and occupational dose levels. (RPIS 0740)

193. Modeling Cellular Responses to Genetic Damage

J.H. Miller

(509) 376-5803

\$160,000

This project contributes to the understanding of health risks from energy-related pollutants in the environment through investigation of the physical and chemical mechanisms for interaction of these agents with the genetic structure of cells. The mammalian genome has a rich variety of structural and dynamic properties that allow DNA sequences to perform their

biological functions. DNA in active genes is subjected to torsional stress that helps produce the strand separation needed for transcription. This project's focus is to investigate the influence of supercoiling and related properties of active chromatin on the production and expression of genetic damage induced by exposure to radiation and chemicals. The researchers have observed in vitro that negative supercoiling increases the sensitivity of plasmid DNA to x-ray-induced strand scission. Computer simulation techniques are being used to investigate mechanisms for this phenomenon and their relation to similar observations with cells. The researchers are examining the effects of bending and sequence-specific torsional deformations on the interaction of DNA with free radicals. The latter may be a mechanism for synergism between damage induced in active genes by chemical adducts and oxidative stress. Hence, understanding how the structure of the genome affects the nature and distribution of damage results in better assessment of the health risks from combined exposure to physical and chemical agents. (RPIS 4173)

194. Radiation Biophysics

J. M. Nelson

(509) 376-5692

\$160,000

Well-defined DNA molecules and carefully characterized mammalian cell systems are studied to assess effects of different ionizing radiations, given at different doses, dose rates, and dose-fractionation schemes, on selected biomolecular targets. Coordinated with currently evolving biophysical and genetic effects models, these studies provide comprehensive tests of biophysical theory relating molecular phenomena and cellular effects to their initiating physical events. Commercially available plasmids and other specifically engineered molecular targets are used to explore specific scientific questions or satisfy specific experimental needs. In this project, Chinese hamster ovary cells and radiation-sensitive mutants derived from these and other cell systems are used to determine radiation response at the cellular level, using survival, mutation, and transformation. Molecular endpoints, such as the probabilities of single- and double-strand breaks, relate damage at the molecular level to cellular effects. The researchers have reported studies showing that survival of supercoiled DNA molecules decreases exponentially with radiation dose and that sensitivity of duplex DNA to single-strand breakage increases with increasing negative superhelicity. The developing cellular and molecular radiation effects models are applicable to other systems. The knowledge gained will ultimately provide a sound basis for extrapolation from relatively high doses and dose rates available in the laboratory to the very low levels encountered in the environment. (RPIS 0741)

Radiation and Chemical Effects: Physical and Chemical Processes

Offsite Grants

Case Western Reserve University

Cleveland, OH 44106

Department of Radiology

195. Ionization in Liquids: Electron Transport and Reactions in Model, Biometric, and Biological Systems

G. Bakale

(216) 844-3547

\$70,000

The objectives of this project are to (1) elucidate the transport and reaction properties of excess electrons in model and biometric systems and (2) apply these results to biological processes that involve electron transfer. The primary ionizing event in radiation physics, chemistry, and biology as well as secondary electron-related processes should thus be clarified through this study, in which pulse-conductivity techniques are used to monitor electron transport and reactions. From this work, a physicochemical carcinogen-screening (PCCS) test has been developed, which identifies chemical carcinogens with an accuracy of ~80 percent for >200 screened chemicals. This accuracy is comparable to, or greater than, that of short-term bioassays designed and routinely used to screen chemical carcinogens. Also, the PCCS test is two- to tenfold more cost-effective than the in vitro screening tests. Efforts to apply the implications of this k_1 -carcinogenicity correlation to radiation-induced biological damage are in progress. (RPIS 9776)

Columbia University

New York, NY 10032

Center for Radiological Research

196. Radiation Physics and Biology

E.J. Hall

M. Zaider

(212) 305-5660

\$705,000

For more than 75 years, the Center for Radiological Research of Columbia University has been concerned with excellence in research in radiological physics and radiation biology. This work has involved the specification and meaning of "absorbed dose" for various ionizing radiations at the subcellular level. Physicists and biologists have worked together to study (1) the physical characterization of energy deposition events, (2) the initiation of molecular change, (3) the modification and/or repair of induced damage, and (4) the frequencies and molecular basis of deleterious inherited change. The pioneering

development of proportional counters to determine patterns of energy deposition has led to the latest achievement, an ultraminiature counter that can simulate nanometer dimensions. The diverse data sets generated by these counters are integrated into models of biophysical action and correlated with computer simulations of charged particle tracks. In this area, studies have led to analysis of electron transportation in "structured water" that is compatible with the water surrounding cellular DNA. The Radiological Research Accelerator Facility at the Nevis Laboratories of Columbia University allows for the systematic study of the biological effects of charged particles and neutrons of defined energy. Studies on the bridge between physics and biology, relating energy deposition events to single cell chromosomal changes, have shown that alpha particles expected from radon daughters do not sustain biological equivalence over their linear energy transfer range, rendering inappropriate a common quality factor. Oncogenic transformation and mutational changes as a function of neutron energy and dose rate have defined an energy range where an inverse (i.e., greater than expected) dose rate effect applies. This has serious implications in radiation protection. The effect has been modeled, embracing all data in a consistent manner, implying a cell cycle stage sensitivity to low dose rate and low energy neutrons. Studies on oncogenic transformants indicate the discovery of a potentially signature-unique radiation-induced oncogene. Such molecular studies point toward future directions with continuing integration between physical, cellular, and molecular aspects of ionizing radiation effects. (RPIS 9787)

Florida State University
Tallahassee, FL 32306

Institute of Molecular Biophysics

197. Energy Transformation in Molecular Electronic Systems

M. Kasha

(904) 644-6452

\$108,000

The work in this laboratory has focused on proton-transfer spectroscopy and dynamics, topics of expanding interest in chemical and especially biological membrane reactions. The researchers have shown the role of triplet potentials in excited state proton-transfer, a highly neglected topic. In favorable energetics, back-transfer from the tautomer triplet has been shown to be a dominant pathway, e.g., in certain aminosalicylates. Other competitive processes to proton-transfer tautomer emission are revealed via the sensitive response of proton-transfer lasing action. The four-level proton-transfer laser has been meticulously investigated because of its intrinsically extraordinary efficiency and its ability to serve as a direct indicator of competitive reactions, e.g., in the contrasting behavior of related pairs of molecules (3-hydroxychromone and 3-hydroxyflavone). Especially prominent has been the competitive excitation of twisted-intramolecular-charge-transfer states in several classes of molecules (e.g., benzanilides) containing twisting amino groups.

The mechanism of "sudden polarization" in the excited state for torsional amino groups, an important process in many biological amino-substituted species, has been interpreted. Picosecond excitation dynamics and differential environmental response to viscosity and dielectric media have permitted resolution of three competitive pathways of excitation: (1) normal, (2) proton-transfer, and (3) charge-transfer. (RPIS 9633)

198. Selective Excitation, Relaxation, and Energy Channelling in Molecular Systems

W.C. Rhodes

(904) 644-1227

\$45,000

Theoretical studies relate molecular structure, spectral structure, and coupling models in determining response, relaxation, and correlated motion. The molecules of interest are primarily biological macromolecules, including synthetic biopolymers. Their properties include circular dichroism (CD), linear absorption spectra, excited-state radiative relaxation, and the channeling of processes (e.g., excitation transfer). Methods of research used in this project include linear response theory, exciton theory, Green operators, reduced equations of motion, and effective operator techniques. The focus is on the role of background (BG) modes (e.g., solvent, substituent groups). Effects of BG modes are formulated by adiabatic modulation, using the quantum Liouville equation. They involve memory terms relating quantum coherence and correlation between the molecule and its BG. Important consequences are (1) kinetic stabilization of states and structures, (2) kinetic enhancement of processes by memory relaxation, (3) sequential channeling of processes, and (4) effects on quantum beats in molecular relaxation. It has also been found that the absorption and CD spectra of helical polymers are sensitive to BG effects. (RPIS 9570)

Louisiana State University
Baton Rouge, LA 70803

Chemistry Department

199. A Physicochemical Study of Some Areas of Fundamental Significance to Biophysics

S.P. McGlynn

D. Kumar

(504) 388-2945

\$123,000

The objective of this project is to study fundamental properties of biologically related molecules using modern spectroscopic techniques. The results are expected to enhance basic understanding of atomic and molecular structures and processes. The research efforts include: (1) density effects on high-*n* Rydberg states; (2) photoelectron spectroscopy of biologically active molecules; (3) development and application of laser photoacoustic and optogalvanic spectroscopy for energy degradation, transient detection, and studies of highly excited states; (4) development of core/orbital separation theorems and correlative algorithms for giant atoms and molecules (i.e., Rydberg states); and (5) determination of micelle structure. (RPIS 9622)

Mount Sinai School of Medicine New York, NY 10029

Department of Physiology and Biophysics

200. Theoretical Studies of Molecular Mechanisms in Radiation Damage to DNA

R. Osman

H. Weinstein

(212) 241-5609

\$95,000

This work is entirely computational and attempts to explore the fundamental molecular processes responsible for DNA damage induced by ionizing radiation. The molecular processes of radical formation in DNA components is being investigated with the theoretical methods of quantum mechanics to elucidate the critical properties that control the primary events in radiation damage to DNA. The properties of peroxy radicals of the sugar moiety are being investigated to explore the importance of the C4' to C5' bond scission in producing strand breaks. The properties of base radicals are being investigated in relation to the proton affinity of the resulting radical ions. The effects of these changes on interbase hydrogen bonding and base pair stability are also being studied. The importance of the process of hydrogen abstraction from the sugar by the base radical is being explored in relation to the transfer of the reactive site from the base to the sugar, leading ultimately to a strand break. Molecular dynamical and molecular mechanical approaches combined with evaluations of solvent effects with a continuum method are also being used in the study of the conformational properties of damaged, strand-broken DNA. The analysis of the kinks produced by the strand break and their comparison to the kinks induced in DNA by the interaction with restriction endonuclease Eco RI are being explored for possible mechanisms by which damaged DNA is recognized by processing enzymes, and for the reasons underlying the enhanced activity of nucleases on damaged DNA. (RPIS 9846)

National Institute of Standards and Technology

Gaithersburg, MD 20899

Ionizing Radiation Division

201. Neutron Interactions with Biological Tissue

R.S. Caswell

J.J. Coyne

(301) 975-5525

\$40,000

The project objective is to obtain information about neutron interactions in tissue through the secondary charged particles produced. Quantitative data detailing physical processes and spectra affecting transfer of energy from neutron radiation to tissue are being obtained from neutron cross section data, range, stopping power, ion yield, straggling information, and geometrical properties. These data are basic to establishing

standards for neutron dose measurements and to providing effective radiation protection for workers. The focus is primarily on the physical interactions of neutrons with tissue. Radiation quality is expressed by the quality factor, Q (considered higher for neutrons than for x rays or gamma rays). The quality of neutrons as a function of their kinetic energy is calculated from the y or linear energy transfer spectra of the secondary charged particles produced.

To improve information needed for neutron radiation protection of workers, energy deposition spectra of neutrons in small volumes are calculated by microdosimetry and nanodosimetry. Computer programs, using both the "analytic method" and the Monte Carlo method, are applied to tissue and to inhomogeneous chambers, such as the Rossi spherical proportional counter (TE ionization chamber). Calculations have been done for neutron energies between thermal and 20 MeV. Future research is expected to concentrate on delta-ray effects, straggling, and improving calculations on the nano-meter-size scale, appropriate for interactions with DNA. (RPIS 9457)

202. Electron Transport Calculations with Biomedical and Environmental Applications

S. Seltzer

(301) 975-5551

\$40,000

The objective of this project is to calculate the interactions of high energy radiations (electrons, photons, heavy charged particles) with atoms and molecules as well as the transport of these radiations through bulk matter (multiple scattering), to obtain radiological physics data for (1) biomedical radiation dosimetry, (2) the assessment of radiation hazards in nuclear and space technology, and (3) the modeling of biological radiation action at the cellular level. Significant results have been obtained in a number of areas: (1) microdosimetric energy-loss straggling and energy-deposition distributions have been calculated for a 1-micron diameter target in a water medium irradiated by protons with energies from 1–20 MeV. These event-size distributions are also applicable to protons released as the result of neutron irradiations. (2) Through the syntheses of all available theoretical and experimental results, a definitive tabulation has been prepared of the cross section for the emission of bremsstrahlung quanta by fast electrons (1 keV–10 GeV, atomic numbers $Z = 1$ to 100). (3) Quantitative results have been obtained which indicate, for a given shield weight, the use of composite shields with an inner layer of lead can considerably improve the protection of spacecraft against electrons and secondary bremsstrahlung. These results have been obtained for spacecraft in typical shuttle and geosynchronous orbits. (4) Proton stopping powers have been tabulated for 72 materials of interest in dosimetry, including 24 elements and 48 compounds and mixtures. The table includes electron and nuclear stopping powers, as well as ranges, for energies from 1 keV to 100 GeV. (5) An up-to-date database and software have been developed for personal computer use. These tools allow photon scattering, absorption, pair production cross sections, and attenuation coefficients to be calculated in a fraction of a minute for any compound or mixture. (RPIS 9456)

University of Nebraska Lincoln, NE 68588

Behlen Laboratory

203. Theory of Relative Biological Effectiveness

R. Katz

(402) 472-2779

\$48,000

The purpose of this study is to develop and test a theory of the relative biological effectiveness of high linear energy transfer (LET) radiations (energetic heavy ions, neutrons) on biological cells and tissues with a focus on such endpoints as cell death, mutations, and transformation toward cancer. It is intended that the theory be quantitative and capable of extrapolation to low doses of both x rays and high LET radiations from experimental measurements at high doses of these radiations. It is also intended that the theory be extended to include the effects of dose rate and biological repair. Although the principal investigator developed and tested the theory in this research, the work is based on experimental data of other investigators worldwide. Progress made in this investigation includes the creation of a parametric, descriptive theory which is widely regarded as the best available at the present time. The present theory does not include dose rate effects, nor does it provide a mechanistic understanding of these phenomena. The investigators are addressing these questions during the course of the current investigations, and are continuing to improve both the structure of the theory and the biological database on which it is tested. The National Aeronautics and Space Administration is applying the theory to study the biological hazards from space radiation to astronauts in space vehicles. These investigations should result in a fully predictive description of biological effect from both low LET (x-rays, gamma-rays, electrons) and high LET radiation at all dose levels. The theory is also applicable to several physical and chemical radiation detectors. Based on the stimulation from this theory, one radiation detector, alanine (where the detection is based on radical production), is now emerging as a nearly tissue equivalent detector of radiation at doses in excess of 1 Gray. (RPIS 9788)

New York University New York, NY 10003

Chemistry Department

204. Mechanisms of Interaction of Radiation with Matter

N.E. Geacintov

M. Pope

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\$300,000

The production of energy, either by fossil fuel combustion or in nuclear power, poses serious environmental health hazards. The combustion of fossil fuels gives rise to airborne particulates containing deposits of mutagenic and carcinogenic

polynuclear aromatic (PNA) compounds. The potentially adverse health effects of ionizing radiation are also sources of serious concern. This project focuses on the fundamental mechanisms and physical and chemical aspects of energy dissipation (especially those processes involving photo-ionization, photo-emission, and electron transfer) in PNA solid particulates, and the interaction mechanisms of mutagenic PNA compounds and ionizing radiation with DNA and other nucleic acids. Specifically, the interaction of both ultraviolet and visible radiation with mechanisms of ionization in solid polycyclic aromatic solids and their nitrated derivatives are being investigated by the highly sensitive Millikan-Pope-Arnold apparatus. In this system, individual electron photo-emission events can be recorded, induced either by steady-state or picosecond laser pulse excitation. The energetics of these processes depend on the different electron/excited energy levels and the relevant polarization energies. The interactions of ionizing radiation and mutagenic and tumorigenic PNA compounds with DNA and related well-defined molecules (short oligonucleotides of defined base composition and sequence) are being investigated using spectroscopic and biochemical techniques. One focus of this research is a detailed comparison of the mechanisms by which environmentally ubiquitous PNA compounds and ionizing radiation cause DNA damage, which can ultimately lead to mutations and tumorigenesis. These investigations are expected to produce a more detailed understanding, on a molecular level, of (1) mechanisms of energy dissipation in photo-excited, energy technology-related PNA solids and molecules and (2) the means by which these mutagenic and tumorigenic compounds cause DNA damage. (RPIS 9472)

Pennsylvania State University University Park, PA 16802

Department of Chemistry

205. Clusters: Elucidating the Dynamics of Ionization Events and Ensuing Reactions in the Condensed Phase

A.W. Castleman, Jr.

(814) 865-7242

\$110,000

One of the most challenging and scientifically exciting problems in the field of chemical physics is to elucidate the influence of solvation, degree of aggregation, and proximity of solute complexes on the reactions and properties of reactive species. Advances in this area potentially have an impact on an enormous range of scientific and applied fields, two of which are radiological physics and atmospheric science. The intent of this program is to provide basic research that contributes to a quantification of the behavior of radionuclides and pollutants associated with advanced energy activities after these materials emanate from their source and are transferred through the environment to the biota and human receptor. The studies provide critical information on problems in radiation

biology by investigating reactions of molecules, which simulate functional groups in biological systems as they follow the absorption of ionizing radiation. Some of the studies on the interaction of electromagnetic radiation with matter are also providing new data for assessing photo-induced transformation of pollutants. These changes include reactions that take place on aerosol particles as well as transformation into aerosols of those species undergoing chemical and physical interaction. The program entails studies along four general lines of research, including: (1) investigation of the dynamics of ionization and the mechanisms of the early-time reactions; (2) studies of electron transfer reactions with attention to the influence of solvation; (3) measurement of the kinetics of ions and reaction intermediates as influenced by solvation; and (4) determination of the structure of solvated reaction centers via spectroscopy, dissociation dynamics, and thermochemistry. (RPIS 9828)

University of Rochester
Rochester, NY 14627

Department of Chemistry

206. Intermolecular Potential Functions from Spectroscopic Properties of Weakly Bound Complexes

J.S. Muenster

(716) 275-4223

\$40,000

This project combines high resolution molecular beam spectroscopy with theoretical modeling to obtain new intermolecular potential functions. Many areas of chemistry are dominated by the interaction energy between individual molecules, including numerous atmospheric and biological processes. Despite the importance of intermolecular potential functions, no routinely used general methods provide the energy of interaction as a function of both the separation and orientation of specific molecules. For example, molecular dynamics simulations of proteins are forced to use extremely crude models to describe the tertiary structure of macromolecules. The present project supports laboratory spectroscopy experiments, which describe the structure and dynamics of small molecular clusters. The insight obtained from these experiments is incorporated into a general potential function model. Model results are then tested with new experiments which, in turn, permit the refinement of the modeling procedures. (RPIS 9632)

**Radiation and Chemical Effects:
Instrumentation Research**

Intramural DOE Laboratories

Ames Laboratory
Ames, IA 50011

Environmental Sciences Program

207. Laser-Based Studies of DNA Damage and Chemical Carcinogenesis

G.J. Small

A.P. D'Silva

(515) 294-3859

\$444,000

The principal objectives of this research program are to (1) refine existing laser techniques and develop new laser techniques for cellular macromolecular damage analysis, (2) determine specific polycyclic aromatic hydrocarbons (PAH) (e.g., BP, 3-methylcholanthrene) of the relative importance of the mono-oxygenation (diol epoxide) and radical cation pathways to DNA damage, and (3) determine the adduct structures associated with each metabolic pathway (these structures will begin with BP), and (4) establish further the utility of laser techniques (e.g., fluorescence line-narrowing spectroscopy) for analysis of DNA damage in humans exposed to complex mixtures of PAH. (RPIS 3991)

Argonne National Laboratory
Argonne, IL 60439

Environmental Research Division

208. Highly Selective Probes of Molecular Photophysics and Photochemistry

P.M. Dehmer

J.L. Dehmer

S.T. Pratt

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\$690,000

Understanding the effects of both nuclear and nonnuclear energy technologies on health and the environment requires the ability to detect and characterize trace quantities of transient, reactive, or excited-state species. Research in this project is directed at devising new methods for laboratory preparation of these species at the quantum-state-specific level, at measuring trace quantities of these species with high selectivity and sensitivity, and at understanding the transformations of these species. Pulsed-laser radiation and synchrotron radiation sources are used to selectively prepare target species for study; ion mass analysis, electron kinetic energy analysis, and/or fluorescence analysis are then used to monitor their evolution, which may include subsequent excitation, intramolecular relax-

ation, fragmentation, and/or chemical reaction. The studies using pulsed-laser radiation sources constitute the primary program emphasis and offer the greatest promise for detailed investigations of molecular photophysics and photochemistry at the quantum-state-specific level. These studies form the scientific basis for future applications of advanced laser probes and are expected to lead to advances in laser technology for chemical measurements, to greatly enhanced selectivity and sensitivity in measurement science, and to advances in understanding the propagation of radiation effects beyond the initial energy deposition. (RPIS 4590)

Brookhaven National Laboratory

Upton, NY 11973

Department of Applied Science

209. Advancements in Atmospheric Tracers and Related Instrumentation

G.I. Senum

R.N. Dietz

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\$112,000

With the increasing diversity of applications of the perfluorocarbon tracers (PFTs) to a range of atmospheric, hydrological, and subsurface leak detection, transport, and dispersion studies, a corresponding need has developed for an ongoing adaptation, modification, and development of the PFT technology. Every newly proposed PFT application increasingly requires the technology to overcome a multitude of deployment, sampling, and analysis problems that must be systematically and efficiently solved for continued and effective applications of the PFT technology. This program is concerned with adapting, modifying, and developing the PFT deployment, sampling, and analyses techniques in a continuing effort to (1) maintain the perfluorocarbon technology at its optimal efficiency for the range of required PFT analysis and (2) to extend the range and diversity of available PFT experiments. This program aims to provide the necessary developments in tracers and instrumentation towards the goal of technology transfer of the PFT technology to the wide range of potential users. (RPIS 4706)

Environmental Measurements Laboratory

New York, NY 10014

Analytical Chemistry Division

210. Natural Radioactivity in the Biosphere

D. Bogen

(212) 620-3637

\$187,000

The most significant radiation dose to the human skeleton is due to ^{210}Pb , through its daughter, ^{210}Po . These isotopes, which are part of the uranium decay series, deliver a radiation dose to cells for the induction of osteogenic sarcoma currently estimated to be a factor of 10 greater than that from ^{226}Ra . The

principal sources of intake of ^{210}Pb are ingestion and inhalation, including cigarette smoking. In addition, inhalation of elevated levels of ^{222}Rn and its progeny, including ^{210}Pb , will substantially increase the lung and skeletal radiation dose. Because ^{210}Pb could be a significant contributor to the U.S. population dose, it is important to establish a reliable database on the levels of naturally occurring, as well as artificial, radionuclides in nonoccupationally exposed people. These benchmark data sets may then be used for epidemiological programs designed to model the past and future risks from exposure both to environmental and occupational levels of alpha-emitting radionuclides. (RPIS 4621)

211. Analytical Development

D. Bogen

(212) 620-3637

\$525,000

This research objective is to develop, evaluate, test, and provide to Environmental Measurements Laboratory (EML) research programs various analytical technologies and expertise necessary to pursue EML research objectives. These research activities are applicable to other DOE scientific activities. For many years, EML has performed this task. EML has also been a recognized authority in radiochemical procedures for (1) determining nuclear pollutants, ion-chromatography, and emission and absorption spectroscopy for estimating inorganic fossil fuel pollutants and (2) for developing gas chromatography and gas chromatography/mass spectrometry techniques for determining energy-related organic pollutants. EML performs a quality assessment program to evaluate DOE contractor performance involved in radioanalytical measurements and consults for DOE in a number of activities, such as the future analytical needs within DOE for environmental restoration and waste management programs. EML also provides onsite reviews of DOE contractor laboratories and expert scientific testimony in litigation involving claims against DOE for environmental or biological damage from its operations. Techniques and methods have been revised and updated for the extraction and determination of chlorinated dioxins, polycyclic aromatic hydrocarbons (PAH), pesticides and furans in soil, sediments, and other environmental materials, using gas chromatography and gas chromatography/mass spectrometry. Under continuing investigation are the speciation, mobility, and solubility of transuranic elements, particularly plutonium, in fresh water ecosystems. Future studies expand the sampling protocols and new or improved methods and techniques to enhance the detection capabilities for selected trace metals, anions, organic acids, heterocyclic PAH, dioxins, and furans. Consistent with all these objectives, new and rapid sample preparation techniques continue to be investigated for a variety of environmental matrices. Studies continue to enhance, update, or modify the computer system and software for data acquisition, reduction, and storage. (RPIS 4817)

212. Fallout Radionuclides in Deposition, Diet, and Bone*M. Heit*

(212) 620-3623

\$256,000

The fallout of nuclear debris, specifically ^{90}Sr , from both atmospheric weapons tests and accidental atmospheric releases is measured to determine the mechanisms of transport and deposition and to verify and correct fallout models. These data are used to identify the global distribution of ^{90}Sr and estimate a continuous global budget and inventory. The long-established Environmental Measurements Laboratory (EML) deposition sampling network may also provide useful data to support studies involving other atmospherically deposited materials. Soil samples are taken in selected geographical areas where the accumulated fallout deposit is uncertain to study the lateral and vertical distribution of radionuclides such as ^{137}Cs , $^{239,240}\text{Pu}$, ^{238}Pu , and ^{241}Am . Optimum site selection requires areas of uniform terrain, but because terrain is not always uniform, new methods are developed to accommodate areas characterized by rough, heterogeneous terrain or forested areas. In recent years, dated sections of lake sediment cores have proved useful for reconstructing the historical deposition patterns of radionuclides from specific sources. This method has been used in Utah and New York to distinguish the deposition patterns of early Nevada testing fallout from global fallout, and in Colorado to show when the major plutonium contamination from resuspended soil occurred in the vicinity of the Rocky Flats Plant. Finally, long-term sampling and analysis of human diet and bone are conducted to investigate the transfer of ^{90}Sr and other radionuclides from deposition to people. The objectives of this project are to correlate body burdens with intake amounts and to follow the long-term behavior of these anthropogenic radionuclides in the environment. (RPIS 4811)

213. Pollutants in Surface and Tropospheric Air*M. Heit*

(212) 620-3623

\$898,000

The Surface Air Sampling Program (SASP) and Radon Monitoring at Bermuda comprise the EML effort to sample and analyze the tropospheric aerosol for radioactivity and other energy-related pollutants. The primary objective of SASP and its network extension, the Remote Atmospheric Measurements Program (RAMP), is to study the spatial and temporal distribution of specific natural and anthropogenic radionuclides in the surface air. To accomplish this objective, high volume air filter samples are collected at about 33 sites located throughout the world. Nine RAMP sites at locations within or bordering the Southern Oceans are incorporated into the SASP sampling network. These sites are equipped with Remote Atmospheric Measurements Systems used to measure the radioactivity on exposed filters directly following sampling and to transmit the resulting information to EML using the Argos communication system aboard National Oceanic and Atmospheric Administration satellites. The filters collected in RAMP are also analyzed for sulfur and nitrogen species, in a collaborative effort with the University of Miami. These species play an important role in

aerosol chemistry and may also have an impact on aerosol-related climate processes. The co-related chemical and radionuclide data are especially useful for the development of global atmospheric transport models. A continuous radon monitor is being installed at the Atmosphere/Ocean Chemistry Experiment site located on Bermuda. Because radon, half-life (3.8 d), is a nonreactive gas that diffuses from the soil, radon can be used as a tracer of continental air masses. The resulting radon data are especially useful for climate modelers to test their global climatological circulation models. The meteorological transport processes associated with elevated concentrations of radon and other tracers of continental air masses are also being studied. This information is especially useful in studies of the chemical transformations in polluted continental air mass aerosols transported to the mid-Atlantic Ocean. Specialized instrumentation is required for measuring particles and gases in the surface air and free troposphere in order to study atmospheric pollutant sources, buildup, and transport. (RPIS 4812)

Radiation Physics Department**214. Radiation Transport and Dosimetry***W. Lowder*

(212) 620-3631

\$345,000

These researchers are developing and evaluating different analytical calculation and experimental techniques for studying radiation propagation and interactions with matter. These techniques are being applied to detailed characterizations of complex radiation fields in terms of physical quantities that eventually may be related to the health risks of exposed individuals, taking into account advances in radiobiological research and biophysical modeling of radiation effects. A multisphere neutron spectro-metry system is being used to determine reference neutron energy spectra at DOE facilities and the exposure of the human population to cosmic-ray neutrons at ground level and at aircraft altitudes. Experimental and theoretical programs in microscopic dosimetry are being initiated to test and apply new methods for determining the characteristics of energy absorption events on the submicrometer scale in charged particle, gamma, and neutron radiation fields. New radiation detection methods are being investigated, including planar microdosimeters and the use of microchips (DRAM). An array of computer codes has been installed and is being extended, tested, and upgraded, taking into account improvements in nuclear models and cross section data. These codes are being applied to studies of boundary effects on radiation field properties, the effects of nuclear recoil and fragmentation in high energy fields, and the determination of organ doses and microdosimetric quantities for an array of incident-particle types and energies and shielding configurations. Collaborations with several DOE national laboratories provide opportunities for critical investigations of improved methods for assessing the potential consequences of human exposure to complex radiation fields, particularly those institutions near accelerators, fission and fusion reactors, at other DOE facilities using or contaminated with radiation sources, and in aircraft and spacecraft exposed to cosmic radiation. (RPIS 0730)

215. Environmental Radiation Research*W. Lowder**(212) 620-3631**\$1,004,000*

The radiation environment is characterized by existing background levels and their variations with time and location, with specific reference to any perturbations that occur because of effluents from nuclear facilities, nuclear weapons tests, or the technological disturbance of natural radioactivity sources. Both experimental and theoretical studies are performed to assess the environmental concentrations of radionuclides and the resultant dose to humans. This involves identifying past, present, or potential releases of specific radionuclides and developing the required detection systems for their measurement at environmental levels. Emphasis is placed on the application of methods for using such measurements to identify and quantify, to the extent possible, the sources and incremental doses attributable to particular activities. This research is designed to maintain sufficient flexibility to provide timely information for DOE use on topical problems. Examples of previous applications include radionuclide measurement and dose assessment following reactor accidents (Three Mile Island and Chernobyl), reconstruction of radiation exposures to populations downwind from the Nevada Test Site, and participation in emergency planning and assessment activities (e.g., the Galileo and Ulysses space probe launches). The experience and capabilities acquired in these programs provide a firm, scientific basis for addressing present and future environmental radiation problems associated with DOE and other Government activities in the nuclear field (e.g., remediation work at former sites and the formulation of state-of-the-art monitoring plans for new production reactors). The scope of efforts will extend to include assessments of possible environmental impacts of non-ionizing radiation and indoor atmospheric pollutants. (RPIS 2840)

216. Radon, Thoron, and the Related Aerosols*W. Lowder**(212) 620-3631**\$1,800,000*

Environmental Measurements Laboratory (EML) provides national and international radon quality assurance programs for radon measurement technology development, characterization of radon and radon progeny sources and exposure, and radon and thoron aerosol in the environment. EML serves as a quality assurance center for U.S. scientists, especially those working under the OHER Radon Research Program. EML is one of four regional reference laboratories in the International Intercomparison and Intercomparison Program for Radon, Thoron, and Daughters Measuring Equipment of the International Atomic Energy Agency, serving as a regional comparison center for North America. Radon measurement technology at EML currently focuses on (1) the development and improvement of small and portable monitoring devices for indoor radon and thoron concentration measurements, (2) the development of instrumentation capable of real-time radon and thoron concentration measurements for application in

locating sources indoors and in tracing the movement of air, (3) the improvement of instruments and methods for measuring the humidity-induced growth of radon progeny in the respiratory tract and its effect on particle size, and (4) the development of the methodology necessary to estimate the bronchial dose directly from radon progeny measurements. Specialized instrumentation and/or modifications of existing equipment are developed for the environmental sampling and laboratory analyses requirements of the EML radon program and the radon research community at large. The goal of characterization studies of radon and radon progeny sources and exposure is to characterize (1) those environmental factors most significant in determining the impact on human health from radon exposure and the consequent dose to the respiratory tract, (2) the relationship between short-term measurements and long-term exposures, (3) the effect of local geological and meteorological factors on the radon source term, and (4) the relative significance of thoron progeny exposure in typical indoor environments. As new measurement technologies are developed and evaluated, they are applied to critical problems of exposure assessment, including the effects of energy conservation technology and practices. The radon and thoron aerosol in the environment project seeks to develop methods for determining the particle size spectra of radon and thoron progeny aerosols over the entire respirable range of 0.5–5,000 nm, to quantify the major sources and sinks that govern these size spectra, and to study the mechanisms of aerosol particle formation in the indoor residential environment. Experimental microdosimetric techniques will be applied to the problem of better defining the interactions of the alpha particles, recoil nuclei, secondary charged particles, and x rays and gamma-rays produced by radon progeny alpha decay in the respiratory tract. The results will be applied to the assessment of radiation damage to the critical cells of the bronchial epithelium. (RPIS 4818)

Idaho National Engineering Laboratory**Idaho Falls, ID 83401****Engineering Research and Applications****217. Neutral Beam Microprobe***J.E. Delmore**(208) 526-2820**\$115,000*

In this program, techniques and instrumentation are being developed for the analysis of surfaces of insulating materials by secondary ion mass spectrometry. Anion and neutral molecular beams are being developed, which are up to 30 times more efficient than atomic beams for the sputtering analysis of organic materials from surfaces. While bombarding the sample with these molecular beams, the extraction lens rapidly alternates between extracting positive and then negative ions from the sample to maintain charge neutrality, and transferring the ions in sequence into the mass spectrometer. With the use of a newly developed data system, both positive and negative secondary ion mass spectra are collected in an interlaced fash-

ion in conjunction with the pulsing of the extraction voltage. This allows even the most heavily insulating specimens to be analyzed in a few minutes using either negative or neutral molecules as the bombarding species, collecting both positive and negative secondary ions from the sample concurrently. This concurrent collection of positive and negative ion spectra gives greatly expanded specificity in the identification of unknown compounds. The ability to dynamically follow spectral changes from sample aging or induced by heat or reaction with gases is inherent in the system. The capability of using negative primary beams on insulating specimens has resulted in broadening the scope of the program to take advantage of newly developed ceramic negative molecular ion sources. The permanent negative ion beams produced from these ceramic sources can be focused to much smaller spot sizes with higher intensity. Past studies developed techniques for the analyses of areas of 1–5 mm diameter spots on insulating surfaces such as plant leaves. The program is currently developing microfocused heavy negative molecular ion beams for applications requiring high spatial resolution, while the applications requiring analyses of larger areas are being spun off to new programs. (RPIS 4738)

Inhalation Toxicology Research Institute Albuquerque, NM 87186

218. Dynamics of Radon Daughter Interactions with Indoor Aerosols

Y.S. Cheng

(505) 845-1034

\$100,000

The purpose of this research is to develop new information regarding the nature and mechanisms of interactions between aerosols and radon progeny. Existing knowledge does not enable accurate projections of radon progeny atmospheres in typical indoor environments. Radon decay products are small cluster particles whose dynamic processes are controlled by diffusion mechanisms; the diffusion coefficient is the most important parameter. Reported values of measured diffusion coefficients for both radon and thoron progeny cover a wide range, from 0.09–0.006 cm²/sec. This inconsistency creates confusion and limits researchers' ability to understand and predict radon progeny and aerosol interactions. Little information is available on the plate-out rates and recoil probabilities of radon progeny attached to indoor aerosols with particle sizes smaller than 0.2 μm. The researchers' approach is first to elucidate individual aerosol processes, including attachment, recoil, and plate-out processes, by using controlled laboratory environments and up-to-date techniques. The results of these initial experiments are essential for settling unresolved issues related to the interaction of radon progeny and aerosols. The results are used to establish mathematical models for predicting these processes under a range of indoor environments. The quantitative information obtained in the initial studies are then incorporated into a room model that describes the dynamic interaction of radon progeny and aerosols in indoor environments. The model is both experimentally validated and is used to predict radon exposure atmospheres for more accurate risk assessments. (RPIS 5008)

Lawrence Berkeley Laboratory Berkeley, CA 94720

Energy and Environmental Division

219. Characterization of Airborne Radon Concentrations

A.J. Gadgil

R.G. Sextro

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\$400,000

This project investigates the sources of indoor radon and the concentrations of indoor radon and radon decay products, with particular attention to processes that affect the migration of radon through soils, entry into buildings, and the build-up and removal processes for radon progeny in indoor air. The five elements of this investigations are to (1) elucidate the factors affecting radon sources and radon entry into, distribution within, and removal from buildings through experimental and theoretical investigations; (2) provide the means to estimate, at a regional level, the potential for elevated indoor radon concentrations, based on regional and local factors such as soil parameters, building construction practices, and meteorological data; (3) characterize radon progeny behavior indoors, including attachment to aerosols and deposition on macro surfaces and other removal processes, by both experimental and theoretical techniques; (4) assemble, examine, and interpret radon and radon progeny data from various sources to provide a critical analysis and integration of current research; and (5) develop methods for estimating long-term average radon concentrations in a specific building, based on a set of short-term diagnostic measurements and interpretive models. (RPIS 4851)

Engineering Division

220. Semiconductor Radiation Detector Technology

J.M. Jaklevic

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\$385,000

The project is researching and developing the design of radiation detectors and associated pulse processing electronics. Particular emphasis is placed on semiconductor detector spectrometer systems for use in a variety of applications. The work includes basic detector material studies, development of improved semiconductor devices, and the design of specialized electronic signal processing techniques. Previous activities in this project have helped establish the foundation for modern detector technology. Recent work has emphasized the importance of radiation damage in semiconductor spectrometers and improved methods for pulse shaping applicable to large volume gamma-ray detectors. Ongoing studies include the development of noninjecting contacts for segmented detectors, investigations of alternative materials, fabrication techniques for room temperature detectors, and the characterization of silicon drift detectors. (RPIS 0708)

221. Semiconductor X-Ray Detectors for Synchrotrons*J.M. Jaklevic**C.S. Rossington**(510) 486-5647***\$275,000**

The project focuses on the development of new semiconductor detectors specifically designed for synchrotron applications. The researchers approach combines existing expertise in semiconductor device fabrication, x-ray analytical measurements, and synchrotron radiation experimentation and includes a close collaboration with Lawrence Berkeley Laboratory experimenters in life sciences and materials research. A primary goal of the effort is the realization of specialized spectrometers capable of exploiting the unique properties of synchrotron radiation sources. Initial studies focused on the development of semiconductor detector systems optimized for low energy photon detection and on detector arrays. An array detector optimized for diffraction studies in structural biology (where precise spatial information is required) has been designed and tested. A second type of array that emphasizes the optimization of energy resolution at high rates for fluorescence Extended X-Ray Absorption Fine Structure applications in dilute biological systems is under development. Fundamental studies into the properties of semiconductor detectors when operated at very low energies are also included in the program. These developments will be undertaken in a collaborative mode in which synchrotron radiation experimenters will be able to effectively exploit the new technology for specific applications. (RPIS 1308)

Lawrence Livermore National Laboratory**Livermore, CA 94550****Environmental Sciences Division****222. Remote Detection of Environmental Contaminants Using Fiber Optic Spectroscopy***S.M. Angel**(510) 422-5765***\$140,000**

The purpose of this research is to develop new spectroscopic methods of chemical analysis for environmental and biomedical applications. Emphasis is placed on remote analysis techniques using fiber optics. These methods will eventually fulfill needs ranging from the initial characterization of the contaminants at a site to the in situ, multipoint monitoring of their movement. The research will focus on optical analytical methods, using the technique of remote fiber spectroscopy (RFS). RFS employs optical fibers to transmit light between a spectroscopic instrument and a remote location in which a measurement is to be made. Spectroscopic analysis is applicable to many types of measurement problems. One technique under exploration is Raman spectroscopy. The use of diode lasers makes it possible to develop small, inexpensive instruments for many applications. Researchers are investigating environmental applications of fluorescence, absorption, Raman, and surface-enhanced Raman spectroscopy using fiber optics. (RPIS 3906)

Oak Ridge National Laboratory**Oak Ridge, TN 37831****Analytical Chemistry Division****223. Isomers and Interactables: Identification of Bio-Adducts***M.V. Buchanan**R.L. Hettich**G.B. Hurst**(615) 574-4862***\$300,000**

Mass spectrometric techniques are being developed for the sensitive detection and unambiguous identification of modified biomolecules, such as DNA and protein adducts, in order to probe the molecular changes that occur in carcinogenesis and mutagenesis. This project has previously demonstrated matrix-assisted laser desorption Fourier transform mass spectrometry (FTMS) for the detection and complete structural characterization of normal and modified oligonucleotides (up to hexamers) at the low picomole level. Work is in progress to refine the laser desorption conditions to extend this technique to larger oligonucleotides. A time-of-flight mass spectrometer is used to optically probe the laser plume to ascertain the factors that affect the matrix-assisted laser desorption event. An electrospray source has been constructed and is being optimized and tested on a quadrupole mass spectrometer prior to interfacing with FTMS. This ionization source, which generates multiple-charged ions for oligonucleotides, is a complementary technique to laser desorption and has been used to examine a variety of nucleic acid constituents and peptides. The project is examining the fundamental parameters that influence the electrospray process. An important component of this research is the continued development of selective gas phase processes that provide detailed structural information, at the isomeric level, for biomolecules. For example, gas phase deuterium exchange reactions and collision-induced dissociation processes are being devised for determining the site of adduct attachment to a nucleoside. Previous success with these analytical methodologies has initiated a number of collaborative interactions with other researchers who have interests in modified nucleic acid constituents, such as photo-induced DNA damage and polycyclic aromatic hydrocarbon nucleotide adducts. Research is focused on development of techniques for the structural characterization of modified biomolecules; however, these methods would also be useful for a broad range of organic compounds as well. (RPIS 4170)

Health and Safety Research Division**224. Medical Physics and Internal Dosimetry***K.F. Eckerman**M. Cristy**G.D. Kerr**D.C. Kocher**R.W. Leggett**(615) 574-6251***\$275,000**

The objective of this project is to further develop methods to define the relationships between radiation exposure and the dose to organs in the body. This objective is being accomplished through modeling (1) the behavior of radionuclides within the body and (2) the deposition of ionizing energy within the radiosensitive tissues from radiation emitted by these radionuclides or from radiation incident upon the body from external sources. Exposure-dose relationships are the cornerstone of radiation protection, the basis of dose reconstruction efforts, and the starting point in risk assessment activities, including comparative evaluations of alternative medical procedures. The major research topics emphasized in the near-term include (1) advancing the state-of-the-art in dosimetric methods and associated database within the medical and radiation protection community, (2) developing dosimetric methodologies to evaluate exposures to the general public (age-specific dosimetry), and (3) providing technical guidance in implementation of the radiation protection guidelines (e.g., interpretation of bioassay measurements). The program, while serving these needs, also serves to unify dosimetric approaches within the radiation protection community. (RPIS 0717)

225. Resonance Ionization Spectroscopy*J.C. Miller**W.R. Garrett**C.H. Chen**M.G. Payne**(615) 574-5898***\$325,000**

Laser-based resonance ionization spectroscopy (RIS) can be used to selectively ionize a large variety of gas phase chemical species in an extremely efficient manner, thereby providing for ultra-sensitive detection and analysis of the subject materials. The scope of this activity includes (1) experimental and theoretical studies of basic processes involved in RIS such as two- and three-photon excitation and multiphoton ionization of atoms and molecules, (2) development of efficient and cost-effective schemes for analysis of specific chemical species, (3) applications of RIS to the development of selective ion sources for mass spectroscopy, (4) studies of effects such as line shifting and broadening related to the fundamentals of the interaction of light with matter, and (5) contributions to the development of RIS methods for use with continuous-wave lasers such as field ionization of Rydberg states. Considerable effort is being devoted to (1) nonlinear optics methods for extending the wavelength region over which RIS can be carried out, (2) physical effects that occur at higher concentrations

where applications of stepwise ionization other than sensitive detection might be made, and (3) the extension of the technique to the mass spectroscopy of large molecules by making use of a combination of infrared light for vibrational excitation followed by near threshold photo-ionization by vacuum ultraviolet photons or by threshold two-photon ionization. These ionization techniques almost always yield only the parent ion, with selectivity being obtained by virtue of the vibrational excitation. (RPIS 1608)

226. Nanosecond and Picosecond Nonlinear Laser Techniques*J.C. Miller**R.N. Compton**(615) 574-6239***\$280,000**

This project encompasses basic and applied research efforts aimed toward the development and use of vacuum ultraviolet (VUV) and infrared (IR) light sources. The VUV sources utilize nonlinear third harmonic generation or, more generally, four-wave mixing of tunable dye laser beams involving one or more near-resonant states in atomic and molecular gases. Similar nonlinear optical techniques (e.g., stimulated electronic Raman scattering, hyper-Raman scattering, four-wave mixing) can generate coherent IR light. Optical "heat pipes" containing metal vapors have been developed and employed to generate IR and VUV radiation with extremely high efficiencies. The UV or IR light from these new and convenient sources are used to perform high resolution fluorescence, absorption, and photoionization studies of atoms, molecules, and free radicals. Nozzle-beam expansions are used to cool the molecules vibrationally and rotationally to take advantage of the narrow bandwidth of the radiation. These innovations could lead to a relatively simple but powerful new breed of instrumentation for analytical applications. A high power, tunable picosecond laser system has allowed extension of these techniques to shorter time (approximately 10 ps) where they may be used to probe the ultrafast dynamics of processes occurring in clusters and in the condensed phase. Laser-surface interactions using picosecond light are used to examine the role of surface plasmons on the efficient ejection of surface atoms, molecules, ions, and electrons. The experimental data will have direct bearing on problems of early-time chemistry in radiological insult to solid and liquid biological materials and to numerous highly reactive species of atmospheric interest. (RPIS 3763)

227. Radiation Calibration Laboratory*C.S. Sims**W.H. Casson**M.A. Buckner**(615) 574-5851***\$350,000**

The purpose of this research is to perform dosimeter intercomparison studies, test personnel radiation dosimeters for compliance with various standards, support low level radiobiology experiments, train radiation dosimetrists and

health physicists, provide radiation calibration services, and perform personnel dosimetry research. The Radiation Calibration Laboratory (RADCAL) is located at the Dosimetry Applications Research (DOSAR) facility. The DOSAR group's technical approach is to (1) maintain RADCAL with well-characterized radiation sources (x-ray, beta, gamma, and neutron), (2) promote development of dosimeters and test their accuracy by conducting intercomparison studies at RADCAL, (3) define training needs by examining test results and develop programs to meet those needs, (4) help radiobiologists and dosimetrists design experiments by providing dosimetry expertise, and (5) perform dosimetry research based on needs that become evident through the various RADCAL activities.

Anticipated benefits associated with this proposal include improved radiation dosimeters, better trained dosimetrists and health physicists, readily available experimental facilities, and transfer of the latest dosimetry-related technology to a variety of practitioners. (RPIS 0714)

228. Pulse-Characterization Neutron Dosimetry

J.E. Turner

R.N. Hamm

(615) 574-0844

\$105,000

This program's objective is to develop the theoretical and experimental foundation for a digital approach to neutron dosimetry and microdosimetry. This approach seeks to characterize the track of a charged recoil particle from a neutron interaction in terms of the numbers of electrons produced in various volume elements of a gas. Knowledge of the position coordinates of every electron produced would constitute complete digital information about a particle track. From such information, properties of a track could be derived such as energy deposited and linear energy transfer, which are needed for neutron dosimetry. A number of microdosimetric quantities, such as proximity functions, and other details of track structure could be obtained. Recent theoretical studies indicate that an optical method could be the basis for detecting electron positions with sufficient resolution for practical neutron dosimetry and microdosimetry applications. If successful, the technique would provide a substantial improvement in neutron dosimetry and spectroscopy and would also enable a number of new measurements in microdosimetry and track structure to be made that have not yet been possible. (RPIS 4227)

229. Dosimetry for New Energy Systems Pollutants

T. Vo-Dinh

G.D. Griffin

M. Uziel

R.B. Gammage

(615) 574-6251

\$370,000

The program objective is to develop novel or improved monitoring technologies to measure chemical and biological indicators of human exposure and health effects associated with energy-related technologies. The research focuses on the

development of portable instruments, cost-effective screening tools, and advanced biochemical sensing technologies for measuring human exposure to key pollutants and related biological compounds in complex mixtures where current techniques are unavailable or inadequate. Research efforts also aim at developing selective and sensitive detection methods for human biochemical responses to hazardous compounds. Laboratory evaluation, field validation, and technology transfer to the commercial sector of these monitoring technologies are integral components of this research program. Examples of research topics in biological and chemical monitor development are (1) cost-effective tools to screen complex chemical and biological samples for biochemical indicators (such as DNA adducts) of human exposure and health effects, (2) a laser-based technique using surface-enhanced Raman spectroscopy of compounds on the surface of metal structures, (3) a room-temperature phosphorescence technique for organic species adsorbed on solid substrates, (4) an antibody-based fiber-optics fluoroimmunosensor for in vivo measurements of biological samples, and (5) noninvasive biological-marker assays aimed at detecting early physiological (e.g., enzymic, macromolecular, and immunological) responses to toxic pollutants. (RPIS 1707)

Pacific Northwest Laboratory

Richland, WA 99352

Chemical Sciences Department

230. Determination of Radon Exposure: Laser Measurements of ^{210}Pb

B.A. Bushaw

(509) 375-3828

\$120,000

^{210}Pb is the first long-lived (22-year half-life) progeny in the decay of ^{222}Rn . It has therefore been suggested that measuring the accumulation of ^{210}Pb in various sample types may help in assessing long-term integrated radon exposure; however, the amounts of ^{210}Pb expected are extremely small (particularly in small biological tissue samples) and fall below the detection limits of conventional radiochemical analysis methods. This project is developing a sensitive, accurate analytical method—based on laser-induced ionization mass spectrometry—that can measure ^{210}Pb at levels relevant to the evaluation of radon exposure. This requires measurement of subfemtogram quantities in the presence of a 10^{11} excess of the stable isotopes. In tissue samples, measuring the ratio of ^{210}Pb to stable isotopes can improve these measurements by normalizing the effect of dietary uptake. This analytical method also facilitates the assessment of past integrated radon exposure within homes and the environment.

The laser-based analytical method uses an isotopically selective double-resonance excitation scheme to ionize Pb atoms generated from samples heated within a vacuum-compatible graphite tube furnace. Two high-resolution continuous wave (cw) dye lasers excite atoms of the isotope to a high-lying Rydberg state via a resonant intermediate state.

This is followed by photoionization of the Rydberg state atoms with a cw CO₂ laser and subsequent analysis of the ions produced with a quadrupole mass spectrometer. The technique can measure both radioactive and stable isotopes and has sufficient selectivity to measure ²¹⁰Pb in the presence of a 10¹³ excess of stable Pb isotopes. Initial measurements have been performed on hair samples from persons with known bedroom radon concentrations and on brain sections from victims of Alzheimer's disease. The measurement of ²¹⁰Pb in hair will include enough samples to assess the correlation (and limits thereof) with radon exposure and to determine the viability of these measurements for assessing long-term integrated radon exposure. Measurements that test the recently postulated correlation between radon exposure and fatty tissue diseases will be extended to bone marrow samples from leukemia victims. Measurements of ²¹⁰Pb plated on the surface of window glass will serve as a basis for determining integrated radon exposures in homes. (RPIS 5010)

Life Sciences Center

231. Biological Effectiveness of Radon Alpha Particles

L.A. Braby

(509) 375-5916

\$250,000

Exposure of lung tissue to alpha particles from radon decay products may be a major contributor to radiation risk for the general public. These exposures occur at low dose rates over long periods of time. Typical doses are so low that only a small fraction of the cells are hit by an alpha particle while most cells remain unirradiated. Risk evaluation is difficult because most experimental evidence has been obtained at higher doses and dose rates. The few experiments that included low dose rates suggest that the induction of tumors in mice increases with decreasing dose rate. This increase is generally unexpected because most adverse effects in cultured cells become less severe when the dose rate is decreased. However, some malignant transformation experiments using cultured cells do show an increased transformation rate with decreasing dose rate. Because transformation of these cultured cells is believed to result if inactivating a suppressor gene or activating an oncogene—processes believed to be important in oncogenesis—this research investigates the dose rate dependence of this process. However, the stochastic nature of charged particle interactions in conventional split-dose irradiations introduces large uncertainties in interpretation of experimental results. These uncertainties are eliminated by using individual charged particles of known energies, delivered through an accelerator-based microbeam system, to produce specified doses in individual cell nuclei. Using this specialized irradiation technique, the kinetics of the dose rate effect in cell transformation is explored and compared with the predictions of models for cancer induction by ionizing radiation. (RPIS 5004)

232. Chernobyl Database

J.A. Mahaffey

R.A. Kennedy

(509) 375-2642

\$75,000

The purpose of this project is to create and maintain an information system to provide usable data for research studies relating to the Chernobyl nuclear accident. The system is the official U.S. repository for information about the Chernobyl accident and its consequences. It includes a library of documents, a computerized bibliography, and computerized diverse radiological measurements with supporting information. Data have been obtained from domestic and foreign organizations and are continuing to be obtained and loaded. The structure and types of these data are analyzed to produce functional requirements for the information system. Structured systems analysis techniques are then used to analyze, design, implement, and document the system. Where possible, the data received are entered into the computerized databases. Presentations and other efforts to inform potential users about the availability of this information resource are being made. Researchers may retrieve data by obtaining a 'portable' microcomputer database application or may request information from project staff on magnetic or printed media. Use of information contained in the system presents an opportunity for researchers to evaluate historical risk, transport, and deposition models previously developed based on data from laboratory experiments, theoretical calculations, computer simulations, and limited real data. (RPIS 4845)

233. Lasers in Environmental Research

R.J. Miller

(509) 375-2968

\$285,000

This program uses high resolution laser spectroscopy to attain a better understanding of the fundamental structural and dynamic properties of atoms and small molecules. The resulting information serves as the basis for developing new, highly selective, and sensitive laser-based technologies to identify and quantify trace environmental contaminants associated with energy production. Studies of atomic isotope shifts, hyperfine splittings, lineshapes, optical pumping, and polarization effects have led to highly efficient, isotope-selective photo-ionization schemes that have been transferred to directed environmental programs. Studies of small molecules have been initiated to provide a detailed description of the interactions of electron spin, nuclear spin, and nuclear rotation angular momenta. These interactions can profoundly influence the structure, decay mechanisms, photoionization dynamics, and chemical reactivity of molecular excited states. In addition to providing a better understanding of fundamental physical interactions of excited state molecules important in atmospheric processes, high resolution studies with continuous wave lasers can lead to highly selective and sensitive measurement technologies for molecular species which can be used in environmental assessment and isotope tracer programs. (RPIS 4360)

234. Capillary Electrophoresis Mass Spectrometry for DNA Adducts*R.D. Smith*

(509) 375-2687

\$275,000

This program aims to develop and explore new, ultra-high resolution separation and sensitive detection methods, amenable to extremely small amounts (<10 femtogram) of previously intractable compounds in complex chemical and biological mixtures. Specifically, the project is developing separation methodologies based upon capillary electrophoresis, which have proven effective in giving high separation efficiencies for inorganic and organic species of ionic and polar character. These methodologies can be applied to the detection and identification of DNA adducts. Another aspect of this work is developing an entirely new approach to mass spectrometric detection based upon continuous (100 percent duty cycle) time-of-flight mass spectrometry (MS) for ultra-sensitive detection with MS. Methods and instrumentation have been developed at Pacific Northwest-Laboratory for the direct combination of capillary electrophoresis with mass spectrometry (CE-MS). The specific aims of this program are to (1) develop and evaluate, and employ new, more sensitive mass spectrometric detectors for chemical constituents separated by CE; and (2) develop new analytical methodologies specifically amenable to the identification of DNA adducts. (RPIS 4752)

**Radiation and Chemical Effects:
Instrumentation Research**

*Offsite Grants***The Aerospace Corporation**

Los Angeles, CA 90009

235. Molecular Detection Using Rydberg, Autoionizing, and Cluster States*J.E. Wessel*

(213) 336-6599

\$115,000

Resonance multiphoton ionization spectroscopy can provide detection sensitivities approaching the single molecule limit. However, the selectivity is highly dependent on the specific excitation process employed and on the molecular properties of the species being detected. The objective of this program is to investigate photoionization processes that provide the optimum combination of sensitivity and selectivity for ultra-sensitive molecular detection. Currently, the approaches being investigated utilize resonance two-photon ionization of molecules cooled in a supersonic expansion, thereby providing increased spectral selectivity relative to ambient temperature methods. Typically, molecular clusters are formed in the

supersonic expansion. The clusters have rich spectra which are being used to evaluate cluster geometries and fundamental intermolecular force fields. Ions of these clusters and their fragmentation products are detected by time-of-flight mass spectrometry, which increases selectivity. These researchers have observed that the ionization processes are greatly enhanced in some clusters, and are now investigating the generality of this phenomenon. Results from the investigations are expected to have important applications in such areas as (1) laser chemistry, (2) environmental monitoring, and (3) fields of chemistry and molecular biology that rely on intermolecular potentials. (RPIS 9454)

California Institute of Technology
Pasadena, CA 91125
Department of Chemistry**236. Resonance Enhanced Multiphoton Ionization Spectra of Molecules and Molecular Spectra***V. McKoy*

(818) 356-6545

\$43,000

Resonance Enhanced Multiphoton Ionization (REMPI) uses laser radiation to (1) excite a molecule from a specific level of its ground state into a specific level of an excited state via absorption of light and (2) subsequently ionize that excited state by further absorption of light before it can decay. The extremely narrow bandwidth of laser radiation makes this technique highly state-selective with respect to the ground and excited states of a molecule. The high state selectivity and background rejection intrinsic to this technique make REMPI a powerful tool for (1) ultrasensitive detection of trace and unstable species, (2) detection of molecules in very specific levels, and (3) exploration of the chemistry of excited states at a state-specific level. The research objective is to carry out theoretical studies of REMPI processes for small molecules and molecular fragments. These studies are to provide a quantitatively robust analysis and prediction of spectral features known to be important in ongoing studies and applications of the technique. Another objective is to determine the rotational and vibrational distributions of molecular ions resulting from REMPI of molecules. Here the emphasis is on identifying anomalous behavior and its underlying mechanisms in these ion distributions. Such behavior introduces serious complications into several of the important applications of REMPI, e.g., extracting state populations from ion signals. By studying these REMPI processes in smaller molecules where robust calculations are feasible, these investigators are providing insight and guidance needed in wider applications of the technique to larger molecular systems. These studies have identified the main mechanisms giving rise to the anomalous ion vibrational distributions resulting from REMPI, as well as schemes for exploiting these mechanisms to produce specific rotational and vibrational distributions of ions using this technique. (RPIS 9604)

Clarkson University

Potsdam, NY 13699

Institute for Environmental Studies

- 237. Radon: Atmospheric Chemistry of Radon Progeny in Laboratory and Real Indoor Atmospheres**
P.K. Hopke
 (315) 268-3861 \$185,000

This project studies the chemical and physical behavior of the ^{218}Po atom immediately following its formation by the alpha decay of radon, to better assess the exposure of individuals to radon decay products in normally occupied homes, and to determine how differences in indoor living conditions such as particle generating activities contribute to differences in the dose per unit exposure. Because small changes in size for activity in the sub-10-nm range result in large changes in the delivered dose per unit exposure, the properties of the radon progeny and the indoor aerosol must be understood for full assessment of exposure to radon progeny and its dose to the cells in the respiratory tract. Two areas of radon progeny behavior are thus being pursued: laboratory studies under controlled conditions to better clarify the fundamental physical and chemical processes that affect a progeny's atmospheric behavior; and studies of actual indoor environments to better assess the exposure of the occupants to the size and concentration of the indoor radioactive aerosol. (RPIS 10317)

Columbia University

New York, NY 10032

Center for Radiological Research

- 238. Nanodosimetry and Nanodosimetric-Based Models of Radiation Action for Radon-Alpha Particles**
M. Zaider
 (212) 305-7387 \$105,000

The purpose of this project is to study the possibility of using nanodosimetric distributions of specific energy towards understanding the biological effects of radon-associated alpha particles and, more generally, high linear energy transfer (LET) radiation. This investigation should be seen as complementary to current epidemiological methods used to estimate radon risks. In particular, the development of a radon-specific model of radiation action should impose significant limitations on the current arbitrary procedures used to extrapolate from higher doses (exposed groups) to lower doses (exposed populations) and therefore reduce systematic uncertainties.

Planned studies include detailed nanodosimetric calculations (for the first time applied to the radon problem), de novo formulation of single-hit multitarget models (a natural for low doses of high LET radiation), and the development of nanodosimetric computational techniques appropriate for the nonuniform geometry of radon exposure. (RPIS 10301)

Comstock, Inc.

Oak Ridge, TN 37831

- 239. Detection of Atmospheric Pollutants Using Infrared Lasers Produced by Stimulated Electron Raman Scattering**
J.E. Talmage
 (615) 483-7690 \$497,652 (2-year funding)

The purpose of this study is to establish the potential for rapid response, high resolution detection, and characterization of infrared active environmental pollutant molecules. Phase I indicated that it will be feasible to use stimulated electronic Raman scattering (SERS) radiation to detect pollutants important in greenhouse effects and acid rain. SERS-generated pulsed tunable infrared (IR) laser beams appear to offer an excellent opportunity for improved instrumentation in such areas as remote measurements, localized sensing, and high sensitivity detection, and may be used in extreme pressure and/or temperature environments. Integration of an optimized optical heat pipe with a pulsed dye laser should result in an effective extension of dye laser range into IR. These Phase I results are expected to lead, in Phase II, to a method that is sufficiently general and sensitive to detect, identify, and quantify both known and as yet unknown pollutants in the environment. Phase II studies development of two new, high resolution IR spectrometers based upon the generation of tunable IR laser light from SERS in metal vapor heat pipes. Visible light from a pulsed tunable dye laser (or broadband amplified stimulated emission) is used to resonantly or near-resonantly excite metal vapors contained in an optical heatpipe that will then be used to generate tunable (or broadband) IR light. One of the spectrometers consists of a tunable, laser-based, SERS-IR source using a high resolution, low divergence, tunable dye laser to generate an ultra-high resolution tunable IR laser beam. The second utilizes broadband, high intensity, pulsed IR light produced from broadband SERS generation that will result in a time-resolved infrared absorption spectrometer based upon a multi-element mercury-cadmium-telluride array.

These IR laser-based instruments should be useful in numerous basic and applied research areas. The tunable IR can be used to detect acid rain pollutants and trace greenhouse gases over extended distances in the atmosphere. The broadband IR light source will be incorporated into an IR absorption instrument capable of detecting transient species (nsec time scale). A significant fraction of dye laser users might find immediate application of these instruments. (SBIR)

Farachem Technology, Inc. Springfield, OH 45505

240. Field-Portable Instrumentation for Metal Analysis

E.J. Taylor

(513) 325-4191

\$49,862

Field-portable instrumentation suitable for onsite metal analysis is needed. Such instrumentation should permit (1) analysis in real time, (2) simultaneous detection of various metals, and (3) detection levels down to parts per billion (ppb). In Phase I, the suitability of an electrochemical measurement concept to achieve these performance characteristics is being established. Phase I consists of the following tasks: (1) use of platinum microelectrodes to study detection of selected metals, (2) fabrication of microsensor band electrode arrays, and (3) evaluation of the microsensor band electrode arrays. Furthermore, it is being demonstrated that the electrode configuration used in this instrument is economical to manufacture.

The commercial applications of metal analysis instrumentation with ppb detection limit and rapid turnaround include (1) characterization, monitoring, and remediation of hazardous waste sites; (2) industrial effluent monitoring, and (3) water monitoring. (SBIR)

Indiana University Bloomington, IN 47402

School of Public and Environmental Affairs

241. Toxic Organic Compounds from Energy Production

R.A. Hites

(812) 855-0193

\$149,000

The goals of this program are to (1) identify potentially toxic organic compounds associated with various combustion effluents, (2) follow the fates of these compounds in the environment, and (3) improve the analytical methodology for measuring the above. The compounds of interest range from polycyclic aromatic hydrocarbons to diesel exhaust to chlorinated dioxins. The pathways and mechanisms by which energy-related agents move through and are modified by the atmosphere are the focus of projects on (1) an improved sampler for semivolatile compounds in the atmosphere, (2) the photodegradation of dioxins and furans, and (3) mobile sources of dioxins and furans. Projects on gas chromatographic tandem mass spectrometry and liquid chromatographic mass spectrometry concentrate on new and more sensitive technologies for chemical measurements. A study of highly chlorinated organic compounds in human tissues focuses on the new area of molecular dosimetry. (RPIS 9660)

University of Michigan Ann Arbor, MI 48109

Department of Chemistry

242. Nanometer Scale Exciton Spectroscopy and Photochemistry: Dynamic Imaging of DNA Structure-Activity Relations and Radiation Signatures

R. Kopelman

(313) 764-7541

\$105,000

These researchers are developing and applying a new, noninvasive technique, combining nanoimaging, nanospectroscopy, and nanophotochemistry. This technique is tailor-made for the in situ and real-time identification of configurations of DNA and the elucidation of structure-activity relationships. The aim is to monitor directly, in space and time, the evolution of the configurational changes and other related transformations that result from radiation and/or chemical damage. Zooming-in on chromatin or other DNA aggregates should show the changes in structure, conformation, and organization that may be relevant to regulating replication and gene expression, as well as to the signatures of pathogenic activity, such as radiation and free-radical chemistry. Specific applications include DNA supercoiling and unwinding under external perturbations, such as irradiation and the addition of known carcinogens. These researchers also want to develop their nanometer-sized exciton tip to a molecular scalpel and miniaturized radiation source in order to study the sensitivity and vulnerability of specific DNA sites. (RPIS 10379)

National Council on Radiation Protection and Measurements Bethesda, MD 30814

243. Development of Recommendations on Radiation Protection and Measurements

C. Meinhold

(301) 657-2652

\$100,000

The National Council Radiation Protections seeks to meet the need for a source of objective scientific information on radiation protection. Recently completed efforts include those on (1) radiation protection for medical and allied health personnel, (2) implementation of ALARA for medical and dental personnel, and (3) calculation of absorbed dose distributions. Work is nearing completion on (1) effects of radiation on aquatic organisms, (2) strontium, and (3) emergency planning.

Research on basic radiation protection criteria, including the risk basis for such criteria, is in an advanced stage as is work on screening models for radioactivity releases to air, surface water, and groundwater. While investigation continues in the operational radiation safety area, important progress has been made on projects concerned with (1) radiation safety in mineral

extraction, (2) calibration of survey instrumentation, and (3) radiation protection records. Other aspects of radionuclides in the environment and internal emitter standards are also being studied. Recently initiated efforts are concerned with (1) collective dose, (2) radionuclide contamination, and (3) radioactive and mixed waste. Areas where important contributions can be made are being identified. Projects where work will be initiated when funding is available include the (1) study of cesium and iodine released to the environment, (2) determination of effective dose equivalent, (3) measurements of radiation accuracy, and (4) design of facilities and equipment for handling unsealed radioactive sources. (RPIS 10202)

National Institute of Standards and Technology

Gaithersburg, MD 20899

Ionizing Radiation Division

244. Radon: Energy Deposition and Radiation Quality of Radon and Radon Daughters

R.S. Caswell

L.R. Karam

(301) 975-5525

\$40,000

This program aims to create a quantitative physical description, at the micrometer and nanometer levels, of the physical interactions of the alpha particles from radon and its daughters with cells at risk in the bronchial epithelium. Alpha-particle energy spectra are being calculated incident upon the cells; energy deposition spectra are calculated in micrometer- and nanometer-sized sites as functions of cell depth, site size, airway diameter, activities of Po-218 and Po-214, and other parameters. This information is now being applied by using biophysical models of radiation effects to predict cell killing, mutations, and cell transformation. These studies can be expected to contribute to a detailed understanding of the mechanisms of the biological effectiveness of the radiations emitted by radon and its progeny. (RPIS 9809)

245. Instrumentation for Nuclear Applications

L. Costrell

(301) 975-5608

\$55,000

The objective of this project is to develop and coordinate nuclear instrumentation standards with resulting economies for the nuclear and radiation measurement fields. Particular emphasis is on: (1) coordination and management of the Nuclear Instrument Module (NIM) system, (2) U.S. activity involving both the CAMAC international standard dataway system and advanced system development, (3) processing and management of national nuclear instrumentation and detector standards, and (4) a modest amount of assistance and consultation services to OHER. Recent accomplishments include the issuance of (1) the updated NIM standard, the predominant instrumentation system in the nuclear and radiation fields

worldwide and (2) numerous national and international nuclear instrumentation standards. Current objectives include updating the standards as the technology advances and continued management and coordination with the national laboratories, university and other laboratories, and industry. (RPIS 9455)

246. Atom Counting Standards and Doppler Free RIMS

J.M.R. Hutchinson

T.B. Lucatorto

(301) 975-5543

\$115,000

This National Institute of Standards and Technology program includes four activities aimed to expand the applicability of resonance ionization spectroscopy (RIS) methods and the availability of isotopic standards: (1) studies of atomization techniques and other factors in RIS for accurate ultra-sensitive isotopic quantitation; (2) measurements of efficiencies and isotopic selectivities of various ionization pathways in elements of environmental, biological, or technological interest, (3) development of a comprehensive data service to provide the pertinent information on RIS schemes for elements of environmental, biological, or technological interest; and (4) establishment of isotope ratio standards for ultra-sensitive isotopic analysis.

The first area of investigation examines isotopic fractionation of the RIS process in connection with the observed ionization bias between even-even and even-odd isotopes as well as the sensitivity of various atomization techniques (e.g., sputtering and glow discharge) to matrix effects. The second area focuses on the possibility of laser methods for isotope separation and the analysis of calcium for use in biomedical studies of bone demineralization. In the third activity, data sheets are produced on a selected group of elements with information that will allow the nonspecialist to quickly ascertain a suitable RIS scheme for elemental analysis. The last effort develops new isotopic standards in response to needs in the analytical community. The work thus far has resulted in a new $^{10}\text{Be}/^{9}\text{Be}$ standard (ratio of order 1:10¹⁰) suitable for application to geological dating in the 10⁶ year range and a new ^{36}Cl standard suitable for measurements made in such fields as hydrology, geology, and cosmochemistry. (RPIS 9533)

Northeastern University

Boston, MA 02115

College of Pharmacy

247. New Fluorescence Methodology for Detecting DNA Adducts

R.W. Giese

(617) 437-3227

\$182,000

Humans are exposed to a diversity of toxic chemical and physical conditions. The conditions that warrant the most attention are those that lead to covalent damage to DNA. This is because such damage, called DNA adducts, is a primary pathway to carcinogenesis and mutagenesis.

This project seeks to establish new methodology for detecting unknown DNA adducts in human samples. The planned new methodology relies on the detection of DNA adducts by using fluorescence labeling/capillary electrophoresis (CE). Ultrasensitivity is to be achieved via laser fluorescence detection. A key challenge is to develop chemical and physical techniques that perform reliably on the trace amounts of adducts encountered in human samples. To date, the following progress has been made: (1) A new method has been developed for isolating DNA from human blood as purified deoxynucleotides. This method avoids the harsh conditions of phenol extraction (a source of artifacts) by employing an ion exchange extraction with enzymatic elution. (2) A convenient, low cost laser fluorescence detector has been built, which can detect 17 picomolar fluorescein by CE. (3) Conditions have been established for the resolution, as well as desired clustering, of normal deoxynucleotides (fluorescein labeled) by CE. (4) The potential of the method to reveal damage to DNA by ionizing radiation has been established by observing a diversity of resolved peaks when a fluorescein-labeled deoxynucleotide is exposed to a ^{60}Co source.

This developing methodology promises to become a powerful new tool for detecting the most critical chemical and physical conditions to which humans are exposed. (RPIS 10230)

Pennsylvania State University
University Park, PA 16802

Department of Chemistry

**248. Radon: Chemical and Physical Processes
Associated with Its Distribution and Effects**

A.W. Castleman, Jr.
(814) 865-7242

\$110,000

Assessing the potential health hazards arising from the presence of radon in indoor environments requires knowledge of their evolving chemical and physical forms. These forms influence transport of radon progeny to the bioreceptor. The chemical and physical transformations affect how much the radon progeny become associated with aerosol particles that can be removed and that can provide a vehicle of transport into the biosystem. Hence, quantifying the mechanisms and rates of the chemical and physical transformations of radon progeny is critical.

The research program emphasizes providing knowledge of the interactions (1) between small, neutral progeny in both the ground and excited states and (2) between ions in their excited state and small aggregates. The small neutral aggregates represent model systems that will quantify the uptake of radon progeny by aerosol particles. Important inter-related components of the program also include (1) studies of the interactions between cluster ions of the progeny and these aggregates and (2) investigations of the interaction between radon progeny and biological molecules, particularly various

functional groups. The cation cluster-anion cluster interactions considered responsible for the formation of the small neutral progeny species detected in certain indoor environments are being investigated. Finally, techniques that allow investigation of aggregates of increasing size are being developed and should lead to an important tool for calibrating conventional aerosol-counting devices for the investigation of radon progeny containing the small aerosol spectrum. (RPIS 9807)

**249. Characterization of Carcinogenic Materials Using
Ion Beams and Lasers**

N. Winograd

(814) 863-0001

\$145,000

This project is developing a novel approach to characterizing and imaging carcinogenic polycyclic aromatic hydrocarbons directly from the solid state. This is important not only for assessment of environmental hazards, but also to establish new techniques for determining chemical changes that may be associated with carcinogenic activity, both in the environment and in biological materials. The method is based on the use of a focused energetic ion beam to desorb the molecule followed by multiphoton resonance ionization and time-of-flight mass analysis. These studies establish the ultimate detection limits of this approach using both well-characterized and complex matrices by optimizing the laser excitation schemes. Because preliminary data indicate these limits are near 10^6 molecules, there is sufficient sensitivity to take advantage of the high spatial resolution of the liquid metal ion source to map the composition of these materials to a spatial resolution approaching $1000 \text{ \AA} \times 1000 \text{ \AA}$. Finally, the project is demonstrating several possible applications of imaging technology to the characterization of carcinogens. These applications include the direct imaging of target molecules on environmental particulates such as fly ash or soot. In addition, the project is investigating the possibility of determining the location of carcinogens and their reactive metabolites directly within a single biological cell. (RPIS 10371)

Physical Sciences, Inc.

Andover, MA 01810

**250. An Imaging Fabry-Perot Spectrometer for Site
Evaluation of Trace Species**

W.J. Marinelli

(508) 689-0003

\$49,990

Field-operable analytical systems are required to evaluate potential hazardous chemical sources and to monitor remediation sites. This project is developing an imaging infrared spectrometer that can rapidly screen field sites to detect the presence of volatile organic compounds from remote locations (either in the air or on the ground). The system employs a close mirror spacing to enhance optical throughput and enable wide spectral coverage at modest resolution. Thermal emission from molecules in the fingerprint region of the spectrum

(825-1,250 cm^{-1}) is detected against a cold atmospheric background using a mercury-cadmium-tellurium array detector. The system employs a wide field of view and hence can be used to screen large areas for emission sources with quantitative results. A compact all-solid-state design, coupled with simple image processing software, allows for the real-time acquisition and processing of spectral data. The data can be used to detect and monitor the concentration of species such as 1,1,1-trichloroethylene, perchloroethylene, carbon tetrachloride, and chloroform, as well as gasoline and diesel fuel components. An experimental demonstration of the imaging spectroradiometer concept and conceptual design of a compact and rugged version of the system is being carried out in Phase I. This effort should demonstrate the technical feasibility of the concept at the laboratory and field level.

The imaging infrared spectrometer would have direct application to the Federal Government and industry as a sensor at hazardous waste sites. Commercial applications of the concept are primarily in the areas of remote monitoring of chemical emissions and in high speed radiometry for measuring temperature for manufacturing applications. The temperature measurement function would be applied to such areas as composite manufacturing and curing, high speed welding and metals processing, and thermal processing of semiconductor wafers. (SBIR)

Princeton University, School of Engineering and Applied Science
Princeton, NJ 08544

Center for Energy and Environmental Studies

251. Exposure to Radon and Radon Progeny in the Indoor Environment

R.H. Socolow
(609) 258-5446

\$90,000

This work measures activity-weighted particle size distribution in occupied houses in conjunction with other relevant parameters to improve the estimate of dose from exposure to radon and radon progeny indoors.

To study and understand building construction and operation both experimentally and theoretically in a small number of buildings, research houses are being instrumented as follows:

- (1) Pressure differentials across each building shell and between the basement and upstairs are measured with differential pressure transducers.
- (2) Basement, living area, attic, and outdoor temperatures are monitored with thermistors.
- (3) Basement, living area, subslab, and basement wall radon concentrations are monitored with passive radon detectors or pumped continuous radon monitors.
- (4) Basement relative humidity and air handler activity are recorded.
- (5) A perfluorocarbon tracer system is used to measure building air exchange rates and interzonal flows.

In addition, a weather station monitors temperature, rainfall, relative humidity, barometric pressure, and wind speed and direction.

Instrumentation to measure the activity-weighted particle size distribution is located in the actual living area of the occupied research house; the large pump associated with this instrument is placed in the basement or outdoors.

Although radon and radon progeny have been measured in many houses, it is the ultrafine aerosol that determines the dose received by sensitive human lung tissue. It is therefore essential to measure the activity-weighted particle size distribution in occupied houses if the dose from exposure to radon is to be quantified. (RPIS 10294)

Department of Mechanical and Aerospace Engineering

252. Reflection Imaging X-Ray Laser Microscope and Its Biological Applications

S. Suckewer
(609) 258-4738

\$331,000

This project is developing an imaging reflection microscope by the (1) testing of the imaging concept of the soft x-ray microscope with Schwarzschild objective in the transmission mode, (2) demonstration of the proof-of-principle for imaging reflection microscope using Schwarzschild objective and soft x-ray laser (SXL) as a source of radiation, (3) design and development of a new condenser based on diffraction plate for matching laser beam with numerical aperture of Schwarzschild objective, (4) optimization parameters of small scale soft x-ray laser in order to adopt this SXL to x-ray microscope, and (5) preparation experiment for testing the exposure and damage of specimen with very short soft x-ray pulses. (RPIS 10542)

University of Southern California
Los Angeles, CA 90089

Department of Physics

253. Theoretical Problems in Laser Spectroscopy of Atoms and Molecules

P. Lambropoulos
(213) 740-7492

\$84,000

The project objective is to develop theoretical methods for understanding and interpreting the interaction of radiation with atoms and molecules. This involves developing techniques for accurately describing atomic structure as well as the dynamics of the interaction of the field with the electrons. Particular emphasis is placed on resonant interactions involving excitation and/or ionization by lasers. The analysis is carried beyond the general theoretical description to the point of providing quantitative interpretation for specific experiments and applications such as isotopic selectivity, determination of isotopic abundances, detection of atoms in complex environments, generation of new wavelengths,

probing of collisions, etc. Recent and ongoing work addresses specific problems on the (1) measurement of isotopic abundances through resonance ionization in Sn and Be, (2) resonant multiphoton ionization and harmonic generation in the rare gases, and (3) the continuing development of theoretical techniques for the description of alkaline earth atoms and their behavior in strong laser fields. (RPIS 9603)

Southwest Sciences, Inc.

Santa Fe, NM 87501

254. Fast Response Instrumentation for Methane Flux Measurements

A.C. Stanton

(505) 984-1322

\$497,792 (2-year funding)

Methane plays an important role in the chemistry of both the troposphere and the stratosphere, and its increasing concentration may have important effects on the global environment. The development of improved instrumentation for real-time measurement of methane fluxes is crucial to characterizing the sources and sinks of this species. This project involves instrumentation based on near-infrared absorption using a commercial laser diode operating near room temperature. An exceptionally rugged and compact instrument for field use is being designed by using fiber optics in place of most conventional optics. Use of high frequency laser detection methods should provide a sensitivity of 1 percent of the average ambient methane background, with 10 Hz response. An advantage of this method is that simultaneous water vapor measurements can be made with the same instrument; this allows methane measurements to be corrected automatically to dry air mixing ratios. In Phase I, a breadboard diode laser instrument demonstrated the detection of ambient methane. Phase II involves optimizing sensitivity and time response so the performance parameters needed to measure methane flux by eddy correlation methods can be achieved. A prototype instrument capable of simultaneous methane and water vapor measurements is being developed. This instrument is used in Phase II to demonstrate measurements of methane fluxes in field environments such as wetlands, rice paddies, or landfills.

This program should result in the development of a compact instrument for real-time measurement of fluxes of methane and water vapor for use in atmospheric research. Such instrumentation could also be applied to mine safety monitoring, natural gas leak detection, and combustion process monitoring and control. The techniques under study are not limited to methane; rather, they are generic to many gas monitoring applications in research and industry. (SBIR)

Spectral Sciences, Inc.

Burlington, MA 01803

255. A Diode-Laser Absorption Remote Concentration Sensor

N. Goldstein

(617) 273-4770

\$500,000 (2-year funding)

This project addresses the need for sensitive, species-selective field instruments for the remote monitoring of trace gas concentrations over long open-air paths. Such instruments are required for a large number of scientific and industrial applications in the areas of pollution monitoring and control, meteorology, and atmospheric chemistry. This project involves the development of a diode-laser absorption remote concentration sensor (DARCS) for measuring trace gas column densities between a transceiver unit and a distant retro-reflector. Wavelength-modulation and harmonic-detection techniques provide automatic control of the diode-laser wavelength, as well as highly sensitive measurement of absorption by a single spectral line. The use of a single, narrow line leads to high selectivity for the species being measured. The low cost, small size, and high reliability of the near-infrared diode lasers, which are used extensively in fiberoptic communications and digital storage and readout systems, permit the DARCS system to be packaged as a man-portable and potentially inexpensive field instrument. In Phase I, a laboratory DARCS system was constructed using AlGaAs diode lasers, and the feasibility of measuring the concentration of minor atmospheric components over kilometer distances and with sub-ppm detection limits was demonstrated. In Phase II, a brassboard prototype sensor is being developed that will be suitable for field measurements of a single atmospheric trace species. This prototype will be used to test the DARCS sensor concept for a variety of trace gases using both AlGaAs and InGaAsP diode lasers. Field trials will then be conducted on a single atmospheric trace species.

The DARCS sensor combines the benefits of low cost, selectivity, sensitivity, portability, and long-term unattended operation, representing a significant advance over currently available commercial instruments. The Phase II prototype sensor could be used for monitoring of pollutants such as nitrogen dioxide and formaldehyde mandated by the Clean Air Act; for research in the temporal variability of climatologically important species such as carbon oxysulfide, carbon dioxide, or methane; for monitoring of emissions from waste dumps, oil fields, and industrial plants; and for use as an alarm system for the fugitive emissions of toxic gases such as hydrogen halides, cyanides, and ammonia. (SBIR)

University of Wisconsin Madison, WI 53706

Department of Medical Physics

256. Fast Neutron Dosimetry

P.M. DeLuca

(608) 262-2171

\$110,000

This research investigates (1) kerma factor determinations of O, Mg, Al, Si, and Fe for 15 to 30 MeV fast neutrons by microdosimetric techniques, (2) applications of high field nuclear magnetic resonance spectroscopy to radiation dosimetry, (3) determination of the production and attenuation of neutrons produced by 70–250 MeV protons striking thick C, Al, Cu, and Fe targets, and (4) response of thermoluminescent materials to very low energy photons. Data for the production of neutrons from bombardment of thick Al, Fe, and Pb targets by 235 MeV protons have been acquired. Event-size spectra have been measured with several different volume tissue-equivalent proportional counters at several concrete depths for emission angles of 0°, 22°, 45°, and 90°. These researchers are analyzing the data to deduce dose-equivalent values and unfolding lengths. Calculations using a modern pre-equilibrium, high energy charged particle transport code are being completed and compared to the data. Measurements of the $^{19}\text{F}(n,2n)$ cross section have been made from 20 to 27 MeV neutron energy. This reaction is allowing precise determination of the fast neutron fluence for kerma factor determinations. Time-of-flight techniques are to be used to characterize the low energy neutron contribution to these kerma measurements. Subsequently, kerma factors for C, O, Mg, Al, Si, and Fe are to be made in the 20 to 30 MeV neutron energy region. Characterization of a methanol-based nuclear magnetic resonance chemical dosimeter has been completed. Several radio frequency pulse solvent suppression procedures have been characterized. Photon doses of ~1 kGy have been employed in this work. New chemical systems, higher field magnets, complex radio frequency pulse excitations for solvent suppression, and FFT techniques for signal analysis are in progress. (RPIS 9485)

Biotechnology: Human Genome

Intramural DOE Laboratories

Ames Laboratory

Ames, IA 50011

Department of Chemistry

257. Quantitation in Electrophoresis Based on Lasers

E.S. Yeung

(515) 294-8062

\$200,000

This project develops novel detection and quantitation techniques in gel and capillary electrophoresis to increase the cost-efficiency, reliability, convenience, sensitivity, and speed of processing DNA fragments. One technique used is indirect fluorometry, in which a fluorescing ion is used to elute the sample, resulting in a large fluorescence background signal throughout the gel. When a component of the sample appears, the fluorescing ion is displaced, and a lower fluorescence signal is observed. This negative signal allows nonfluorescing species, such as DNA fragments, to be detected with the high sensitivity normally associated only with fluorescing species. Migration errors are eliminated because tags are absent. Sample preparation for electrophoresis and sample collection for subsequent sequencing are also simplified.

Researchers have demonstrated that restriction fragments in the range of 0.1–23 kb can be (1) separated by this method and (2) detected down to the pg level in capillary electrophoresis and down to the ng level in slab gel electrophoresis. A complete electrophoretogram can be obtained in a few minutes using capillary electrophoresis.

Novel ways to improve the speed and reliability of imaging schemes for use in mapping and sequencing are also being explored. A charged-coupled detection device and a unique background correction algorithm can be employed to image native DNA in slab gels, using the intrinsic ultraviolet absorption of the bases at concentration levels comparable to those in standard protocols. This technique is being applied to the real-time monitoring of pulsed-field gel electrophoresis so that interactive control can be implemented by field programming during the separation.

For sensitive laser-excited fluorescence detection in capillary electrophoresis, a multiplex approach that does not require critical optical alignment is being developed. Hundreds of parallel capillaries can be monitored at the same time, thus speeding up DNA sequencing. (RPIS 4922)

Argonne National Laboratory
Argonne, IL 60439

Biological and Biomedical Research Division

258. An Integral Approach to Genome Studies

R. Crkvenjakov

R. Drmanac

(708) 252-3161

\$870,000

Sequencing by hybridization (SBH) is currently the frontrunner among the methods being developed to significantly increase the speed of DNA sequencing for the Human Genome Initiative. After undergoing successful exploratory studies and the determination in a blind test of 340 bp of sequence without error, SBH is being implemented on complex model systems. A data production line having a minimal throughput of 40,000 clones hybridized with five probes per day is being combined and tested. The first data are being collected on M13 clones either covering cosmid clones or representing a part of human expressed sequences (cDNAs). These data allow the ordering of M13 clones and the cataloging of the new genes, and they provide characterized genomic and cDNA M13 clones for mapping and sequencing by existing methods. The data also serves as the basis for testing and improving SBH algorithms and software being developed on simulated data. Production should reach the capacity of one million M13 clones hybridized with 2,000 probes per year, thus achieving the theoretical potential of SBH: sequencing speeds of one million bases per day per laboratory. This methodology, once available, will allow a new approach in genome structural and functional analysis. This approach consists of progressive sequencing in parallel of related genomic regions or whole genomes that have a similarity of more than 65 percent by integrating partial sequences obtained by 6- to 8-mer probes, already known sequences, and raw sequences generated by gel methods. The latter targets members of new gene families (and other families of similar sequences) recognized on the basis of partial sequences obtained by SBH. The projected sequencing efficiency by the SBH variant described here is 100 million bp per year per laboratory. (RPIS 5485)

Division of Mathematics and Computer Science

259. Computational Support for Sequence Analysis Projects

R. Overbeek

(708) 252-7856

\$259,000

Genome sequencing projects involve complex, time consuming, and often computationally intensive projects. This research explores ways in which logic programming can help the molecular biologist attack such problems more easily and more effectively. Particular attention is given to recent developments in bilingual programming and to the use of parallel processors. Tools are being designed that can be used in the analysis of genome sequencing data and in the interpretation of phylogenetic trees. (RPIS 5193)

Brookhaven National Laboratory
Upton, NY 11973

260. Rapid Preparation of DNA for Automated Sequencing

J.J. Dunn

F.W. Studier

(516) 282-3012

\$341,000

Large scale genomic DNA sequencing needs a reliable supply of template DNAs suitable for the particular sequencing strategy employed. Techniques to prepare double-stranded DNA templates the size of cosmid DNAs about 40 kilobase pairs (kbp) are being developed. These DNAs would be sequenced directly by primer walking rather than by subcloning into other vectors. Bacteriophage T7 efficiently replicates and packages DNAs that carry appropriate signals; it may provide a convenient cloning and amplification system for obtaining substantial amounts of 40-kbp DNA for genome sequencing. The ability of normal and mutant T7 replication enzymes to improve enzymatic sequencing reactions and to amplify genomic DNA directly without cloning is being tested. (RPIS 5040)

Biology Department

261. High Resolution DNA Mapping by Scanning Transmission Electron Microscopy

J.F. Hairfeld

(516) 282-3372

\$225,000

The use of scanning transmission electron microscopy (STEM) to map and sequence DNA directly may complement the fast-growing technology of automatic sequencing. The advantages of a direct physical microscopy approach to sequencing include the ability to use very long fragments (10^3 to 10^6 bp) and to sequence them several orders of magnitude faster than would be possible with chemical methods. In addition, long DNA pieces do not present the problems associated with repetitive sequences. Although direct sequencing may be difficult to achieve with microscopy, high resolution mapping is currently attainable. Again, potential use of pieces $\sim 10^4$ bp yields immediate advantages in the speed of discerning sequence organization.

Preliminary results were obtained using the following test system. A 622-bp sequence from pBR321 was excised with restriction enzymes and purified. A 128-bp fragment from the T7 virus was inserted at position 276 of the plasmid fragment, making a total of 720 bp. Denaturing and renaturing equal quantities of the 622-bp and 720-bp fragments resulted in a 50 percent formation of heteroduplexes, in which one 622-bp strand paired with a 720-bp strand and left the extra bases as a single-stranded loop. The next step involved synthesizing a 26-mer oligonucleotide complementary to a region of the single-stranded insert. This oligonucleotide was chemically modified by adding a sulfhydryl to the 5 prime end and covalently attaching an undecagold cluster to it. The undecagold cluster contains 11 gold atoms and provides a small high resolution

marker visible in STEM; it has a gold core 0.8 nm in size. The oligonucleotides and heteroduplexes were then mixed under renaturing conditions and examined with STEM. A kink was observed at the 128-bp single-stranded insert position in the control heteroduplexes (with no gold clusters); also, total length and length to the insert were inconsistent with the proposed model. When the gold-oligonucleotide was hybridized, the gold cluster was visible as a tiny bright dot at the "V" vertex of the DNA. The gold cluster was about 10 Å (3 bp) from the base it labeled (3 bp); the accuracy of positioning a base from the end of DNA segments with STEM is ~2 bp. A total potential positional accuracy of 3-5 bp should prove useful in physical mapping.

Further work demonstrates RNA labeling. Yeast tRNA^{Phe} was altered to enzymatically introduce 2thiocytidine (s²C) at position 75. This was covalently coupled to an undecagold cluster. *Escherichia coli* tRNA^{Arg} with a naturally occurring s²C at position 32 in the anticodon region was labeled similarly; this alteration required denaturation. The nucleic acid labels used are the smallest found to be stable in an electron microscope having a resolution of about 1 nm (3 bp). Their visualization by STEM provides the first example of high resolution RNA labeling by electron microscopy.

Another project involved labeling a palindromic 12-mer having a 5 prime sulfhydryl with the undecagold cluster. Upon renaturation, one would expect to observe a short double-stranded piece of DNA separating a gold cluster at each end; this was borne out in preliminary data, which showed pairs of clusters at the appropriate distance. This is the first time that a piece of DNA as small as a 12-mer could be discerned and identified directly with these labels in the electron microscope (EM).

These test cases demonstrate the potential of labeling specific bases for EM to obtain high resolution structural information for mapping. (RPIS 4896)

262. Large Scale DNA Sequencing with a Primer Library
F.W. Studier
J.J. Dunn
(516) 282-3390 \$500,000

This project is developing a DNA sequencing capacity that can contribute significantly to the 15-year goal of sequencing the human genome. The strategy is to sequence 40-kbp clones (such as cosmids) directly by primer walking, using only primers from a library. If successful, this approach would improve efficiency and reduce costs by at least an order of magnitude over current practice. It would also provide the basis for developing automated sequencing machines capable of generating perhaps 100,000 nucleotides of sequence per hour. For this strategy to succeed, either primers as short as nonamers or decamers must be able to prime sequencing reactions specifically and reliably, or some simple means to join shorter primers to make longer ones must be devised. Researchers are seeking conditions or determining rules that make the primer-library approach practical and are developing primer walking with

longer primers. Even if the primer-library approach proves impractical, conventional primer walking, together with a machine that simultaneously synthesizes small amounts of many primers, could result in a substantial improvement over current practice. (RPIS 5520)

263. New Approaches to DNA Mapping: Synthetic Endonucleases
B.M. Sutherland
(516) 282-3293 \$347,000

Recognition and mapping of functionally important DNA regions (e.g., regulatory and coding regions, initiation sequences) can be greatly facilitated by specific DNA cleavage at such sites. Synthetic endonucleases able to cleave at regions of functional importance are being created by coupling DNA site-specific binding proteins via linker arms to light-activatable cleaving moieties; specific binding function is provided by the DNA-binding protein, and cleavage activity by the activatable cleaving molecules. A prototype system of Rose Bengal coupled via a hexanoic acid linker to a DNA lesion site-specific monoclonal antibody is being developed for other specific DNA-binding proteins, including T7 ribonucleic acid polymerase and mammalian transcription initiation factors. Additional cleaving groups, linkers, and coupling procedures are being developed to optimize reaction with DNA-binding proteins of differing surface groups and reactivities. The specificity and efficiency of binding and cleavage of each synthetic endonuclease are evaluated using a new electronic imaging system. Their utility in mapping, cloning, and sequencing human DNA is evaluated. (RPIS 5039)

Chemistry Department

264. Protein Data Bank Operations
T.F. Koetzle
E.E. Abola
(516) 282-4384 \$225,000

The Protein Data Bank (PDB) is an archival computer database of three-dimensional structures of biological macromolecules serving the international scientific community. The database, which is a unique resource in structural biology, contains atomic coordinates, bibliographic citations, and primary sequence and secondary structure information as well as crystallographic structure factors and two-dimensional nuclear magnetic resonance (NMR) experimental data. Information is available on protein, DNA, RNA, virus, and carbohydrate structures. Most of these data are derived from diffraction studies. Structures derived from solution NMR are now also being distributed, and the number of these structures is expected to increase dramatically.

A large amount of effort is expended in the standardization and checking of data that are deposited in PDB. Each entry is checked to ensure that it conforms in all details to the PDB format and is analyzed carefully to verify that any errors or

abnormal features in the geometry of the macromolecule are corrected or documented. Users depend on the reliability of data, and the information must be stored in a way that conforms to accepted conventions. Every new atomic coordinate set is checked extensively, using computer programs written by PDB staff. The resulting diagnostics are returned to depositors for their comments before the data are released to the public.

The data distributed by PDB is used extensively by laboratories working in areas of biomedical research. Notable among these are drug design investigations and protein engineering projects as well as studies aimed at understanding the mechanisms involved in folding protein molecules into their native structures. Recent findings indicate that sequence alignment of distantly related proteins is facilitated by the use of three-dimensional structure data, so that laboratories engaged in sequencing efforts increasingly require access to PDB. For large scale sequencing efforts such as the Human Genome Initiative, such access is clearly essential. Extensive use of PDB is also seen in computer science and informatics research dealing with issues regarding access to information stored in massive and heterogeneous biological databases. (RPIS 5520)

Lawrence Berkeley Laboratory Berkeley, CA 94720

265. Human Genome Center

J.D. Rine

(510) 642-7047

\$6,050,000

The Lawrence Berkeley Laboratory (LBL) Genome Center has active projects in genomic DNA sequencing, genetic mapping, physical mapping, and cDNA isolation and analysis. Each of these efforts involves close interactions among the biology, instrumentation and automation, and informatics groups. The LBL Human Genome Center has taken a leading role in high throughput genomic DNA sequencing through the conception, design, and implementation of the first successful directed sequencing of a large segment of genomic DNA. LBL has chosen genomic DNA sequencing as a major focus for the coming years, while maintaining a balanced effort in the other three areas of genome research.

Major biological goals for the next few years are to (1) assemble physical maps of complete chromosome arms rooted in templates appropriate for sequencing and (2) develop the capacity to produce genomic sequence of multiple megabases per year. One target is the long arm of chromosome 21, for which researchers have already isolated sufficient P1 clones from a biologically rich region to feed the sequencing assembly line. The major instrumentation and informatics goal is to develop the degree of automation needed to produce an effective sequencing assembly line and to capture, assemble, analyze, and distribute massive amounts of sequence information.

Researchers' physical mapping efforts are targeted to those clones that have a reasonable chance of being sequencing templates for a directed strategy. After a variety of cloning vectors were considered, it was decided that bacteriophage P1 and its related vectors offer the best available source of

sequencing template. A strategy of manipulating P1 clones into gene-sized fragments ordered in a minimally overlapping set of smaller clones has been developed and proven.

The rapid success in sequencing (80kb in 4 months with 4 full-time equivalent) was made possible by the development of instrumentation that supports these efforts. The automation of colony picking, polymerase chain reaction (PCR) setup, sequencing reaction setup, gel loading, and agarose gel analysis is either complete or near completion. Immediate goals are to complete the development of a large scale, extensible PCR thermocycler, a DNA preparation instrument, and a large scale oligonucleotide synthesizer.

The informatics support of the large scale mapping and sequencing work has received much benefit from a focus on the AceDB kernel and ancillary programs. This has been achieved through collaborative work with the Medical Research Council (United Kingdom) and the Centre d'Etude Polymorphisme Humain (France). In addition, researchers are working closely with a Baylor group on a sequence assembly package that has been designed and implemented to maximally benefit from the directed approach to DNA sequence. (RPIS 4981(A-O))

266. Human Genome Center/Coordinating Committee **Administration**

S. Spengler

(510) 486-5874

\$542,000

The Human Genome Coordinating Committee (HGCC) provides several services for the DOE Human Genome Program. These services include making arrangements for and covering Joint DOE-National Institutes of Health Human Genome Program meetings, preparing materials for and arranging meetings of HGCC and its working groups and subcommittees, and preparing meeting and workshop reports. (RPIS 5505)

Cell and Molecular Biology Division

267. Human Genome Center/Isolation of Chromosome **21 cDNA Clones**

J. Cheng

(510) 486-6549

A cDNA selection method for the rapid enrichment and identification of coding sequences in a large segment of genomic DNA has been developed. The basis of this selection procedure is the hybridization of an entire library of cDNAs to immobilized genomic clones. Nonspecific hybrids are eliminated, and hybridized cDNA molecules are eluted and amplified by polymerase chain reaction. Large and ordered genomic clones are becoming available; in addition, finer resolution genetic maps of chromosomes are being built for localizing genes responsible for genetic traits. The proposed cDNA selection method allows quick identification of genes in a defined genomic DNA segment. Researchers are also testing the feasibility of extending this technology to the entire chromosome. (RPIS 4981(A))

268. Human Genome Center/Rapid Isolation and Organization of Chromosome 21 YAC Clones

J. Cheng

(510) 486-6549

The short term goal of the human chromosome 21 cloning and mapping project is to generate a 10-megabase (Mb) yeast artificial chromosome (YAC) contig from the q terminus. The approach is based on hybridizations of pooled YAC libraries on dot blots with pool-specific DNA probes. This method also allows quick contig-building of the identified clones. The process of building this 10-Mb YAC contig can be divided into two experimental phases. In the first phase, researchers will focus on screening the YAC clones to achieve 90-percent coverage of the 10-Mb region by using DNA probes derived from the regional assigned cosmid clones. The second phase of the task will be focusing on the isolation of clones to achieve closure. In this phase, end probes derived from each isolated YAC contig will be used to identify their overlapping clones. (RPIS 4981(B))

269. Human Genome Center/Rapid Isolation and Organization of Chromosome 21 YAC Clones

J. Cheng

(510) 486-6549

The short term goal of the human chromosome 21 cloning and mapping project is to generate a 10-megabase (Mb) yeast artificial chromosome (YAC) contig from the q terminus. The approach is based on hybridizations of pooled YAC libraries on dot blots with pool-specific DNA probes. This method also allows quick contig-building of the identified clones. The process of building this 10-Mb YAC contig can be divided into two experimental phases. In the first phase, researchers will focus on screening the YAC clones to achieve 90-percent coverage of the 10-Mb region by using DNA probes derived from the regional assigned cosmid clones. The second phase of the task will be focusing on the isolation of clones to achieve closure. In this phase, end probes derived from each isolated YAC contig will be used to identify their overlapping clones. (RPIS 4981(C))

270. Human Genome Center/Chromosome 21 Physical Mapping

J.C. Gingrich

(510) 486-6549

The goals of the Human Genome Project are to (1) create physical and genetic maps of chromosomes; (2) determine the sequence of human (and selected model organism) DNA; and (3) develop the technologies necessary to achieve these objectives. This project takes one approach to creating the physical map of chromosomes in this case, human chromosome 21.

By virtue of being the smallest human chromosome (~50Mb), chromosome 21 is an ideal model for testing approaches to a mammalian chromosome-size physical mapping

effort. The effort described here utilizes large chromosome 21 DNA inserts in yeast artificial chromosomes (YACs) to initially build a 10Mb contig at the end of the q arm of the chromosome. Knowledge and resources gained from this first contig-building effort will then be used to generate additional large contigs of the chromosome, with the ultimate goal of complete closure of the chromosome into one ordered YAC contig.

First, a fluorescence in-situ hybridization (FISH) map of the chromosome is generated. The 10Mb region of initial interest is defined from the FISH map as the region approximately terminal to the markers S55, ERG, and ETS. The FISH map is then used to aid in the regional assignment of new probes from this region. For the initial 10Mb goal, approximately 100 region-specific probes are being generated from YACs and cosmids that are regionally assigned by FISH. Chromosome 21 YACs from the 10Mb region will then be identified by a variety of polymerase chain reaction and Southern hybridization approaches in four YAC libraries that have been collected. The YACs will be further characterized by size and restriction fragment analysis, and contigs will be built based on the presence of one or more of the probe sequences in each of the YACs. Finally, enclosure of the YACs into larger contigs will be achieved using contig-end probes. This task relies heavily on biological methods development and the applications of robotics and computers to help in the characterization and tracking of large numbers of clones and large amounts of data on these clones. (RPIS 4981(D))

271. Human Genome Center/Large Scale DNA Sequencing

M. Palazzolo

C. Martin

(510) 486-5909

Despite recent advances, the ability to sequence at the level and cost required to meet the stated goals of the Human Genome Project has not yet been achieved. Even the most advanced groups are more than two orders of magnitude away from the efficiency required from the point of view of finished sequence throughput. Specifically, it is now possible for a dedicated group to generate 100-200 kb of finished sequence per year. Furthermore, the cost of obtaining this sequence (about \$6.00/base) is at least an order of magnitude greater than the cost at which it is considered economically feasible to anticipate funding experiments aimed at elucidating the entire human sequence.

One of the major remaining difficulties in large scale sequencing is the gap between the size of the mapping clone (the 40-kb cosmid, the 100-kb PI, or the 200-kb yeast artificial chromosome) and the 450-base pair (bp) stretch of DNA that can be routinely sequenced from a single priming site. In other words, the problem is how to inexpensively and rapidly create or identify sequencing priming sites every 450 bp in a large DNA fragment. This project is using a series of molecular biological and molecular genetic procedures to efficiently deliver a set of nonoverlapping templates to the automated sequencers in order to better approach the theoretical throughput of these machines. (RPIS 4981(L))

272. Human Genome Center/100 Megabase Physical Mapping

M. Palazzolo

C. Martin

(510) 486-5909

In collaboration with the Automation Group at the Lawrence Berkeley Laboratory Human Genome Center, researchers are attempting to develop automated nonrandom methods for physical mapping. This project will use a nonrandom sequence-tagged site (STS) selection scheme and subsequent STS content mapping. This approach promises to reduce the time and cost required to build a high quality physical map. Computer simulations of contig-building experiments based on these procedures suggest that a nonrandom STS strategy that uses paired probes requires threefold to fourfold fewer STS assays than are required in random and nonpaired approaches. Furthermore, the selection algorithm also results in a map that has both greater genome coverage and a larger average contig size. Upon completion, this map should provide coverage of 99 percent of the 'clonable' portion of the 100-megabase target genome in a form that makes the cloned contigs available for subsequent large scale sequencing. In addition, such a map is also available to generate greater resolution based on the localization of markers that incorporate large amounts of biological information. This work is testing a number of important methodologies (that are not being examined in most other genome projects), including mapping inserts cloned into P1-pacmids, nonrandom STS selection strategies, and computer-assisted automated STS mapping. Because the selected target genome is approximately the size of an average human chromosome, this work is an ideal test of a variety of mapping procedures in which the target genome is only moderately complex. (RPIS 4981(M))

Engineering Division

273. Sequencing by Hybridization

T.M. Brennan

(415) 723-6277

\$150,000

This research examines a method to produce very large, high density arrays of oligonucleotides for use in hybridization sequencing. These arrays of oligonucleotides are synthesized by massively parallel chemical reactions on glass plates. Each element in the array is separated from its nearest neighbors by a surface tension wall. The synthetic reactions are carried out on a picoliter scale. The specific nucleotides are delivered to each array element by arrays of piezoelectric pumps similar to an ink jet printer. A stable hydroxyalkyl group bound to the plate acts as the 5 prime-OH surrogate on which to initiate strand synthesis. This linker arm enables removal of purine and pyrimidine blocking groups without cleavage of the oligonucleotide from the support.

A relatively simple machine should be able to produce the full 1,024 x 1,024 array of 10-mers at the rate of one plate or 10⁶ oligonucleotides per hour. (RPIS 5676)

274. Human Genome Center/Atomic Force Microscopy/Scanning Tunneling Microscopy

J.M. Jaklevic

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In this task, the techniques of scanning tunneling microscopy (STM) and atomic force microscopy (AFM) are being investigated for use in the mapping and sequencing of DNA fragments. The approach is to employ the atomic resolution capabilities of these instruments to directly detect the physical morphology of individual DNA strands attached to suitable substrates. To optimize performance, specialized STM/AFM instrumentation is being designed, and methods are being developed for the efficient manipulation and attachment of DNA to the substrate prior to imaging. (RPIS 4981(E))

275. Human Genome Center/Automation and Robotics In Support of the Human Genome Center

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This task introduces appropriate automation and robotics into those techniques of molecular biology that are important tools for genome research. The two overall goals of the automation effort are—

(1) To identify those procedures within large scale experiments that are potential bottlenecks and are amenable to automation.

(2) To work closely with biologists and computer specialists to develop and implement solutions to the bottlenecks in an integrated system. The system must address problems of scale in order to cope with the requirements of the Center and the Human Genome Project itself. It must permit early starts and allow for modifications during its lifecycle in order to accommodate improved technology.

To achieve these goals, a series of automation modules is being developed. Each is intended to operate in standalone mode or as part of an integrated automation system that uses robots to transport materials (labware and DNA source material) to and from the different devices. (RPIS 4981(F))

276. Human Genome Center/Fluorescent Detection of Biological Probes

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In all areas of the Human Genome Program, genetic mapping, physical mapping and sequencing, the detection and sizing of DNA fragments, and the identification of hybridization probes attached to DNA fragments are of major importance. In many cases, these operations are carried out using ethidium bromide ultraviolet fluorescence and probes with radioisotopic labels such as ^{32}P . The continued use of these reporters in the large volumes anticipated for the Human Genome Program constitutes a serious environmental hazard and associated waste disposal problem. In the past, radioisotopic labels have been used because of their high sensitivity. With the advent of polymerase chain reaction technology, new protocols in which sensitivity is less of an issue have been developed, making it possible to use alternative reporters—such as fluorescent dyes—that are environmentally safer and offer new performance features. In particular, researchers are investigating the application to the Program of multiwavelength-emitting fluorescent labels, both to determine optimized protocols for their use and to develop instrumentation to detect them in various media such as microtiter plate wells, membranes, and gels. Once developed, the techniques will be applied directly to the Program, replacing existing methods wherever applicable. Initially, fluorescent tags similar to those used in existing fluorescent sequencing machines will be employed, but other labels—including dyes with long lifetimes—will be investigated. Other methodologies for fluorescent detection, such as evanescent wave excitation, are also being studied. (RPIS 4981(G))

Human Genome Center and Engineering Division

277. Advanced Detectors for Mass Spectroscopy

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\$195,000

The application of mass spectrometry to the separation of macromolecules is currently limited by the maximum size that can be efficiently measured, a limitation that will seriously affect future DNA mapping and sequencing efforts. Although methods exist for mobilizing and accelerating intact, charged molecular species with a mass of 200,000 Da, conventional ion detectors are inefficient for these large ions. These detectors rely primarily on the multiplication of secondary electrons generated by the primary molecular ion's high velocity impact—a process that becomes less efficient for heavier molecular ions.

The project is investigating the fundamental parameters that limit the use of secondary electron emission for efficiently detecting large ions. The goal is to extend this approach to the limits of applicability. In addition, alternative methods are

being explored for efficiently detecting large molecules. These methods include hybrid detectors, in which the primary ion is used to produce secondary, smaller ions through collision cascades; cryogenic bolometric devices, in which the energy of the ion is determined directly without reference to ionization processes; and semiconductor diode detectors, in which the thermal spike generated by the heavy ion impulse is electronically measured. In each case, feasibility studies are being conducted, followed by practical implementation and testing where appropriate. The long-term goal of the project is to design a mass spectrometer capable of efficiently operating in the mass range above 100,000 Da and optimized for measuring large DNA fragments. (RPIS 5608)

Information and Computing Sciences Division

278. Human Genome Center/Database Tools for Scientific Applications

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Scientific applications, such as molecular biology applications, generate large amounts of data that must be maintained and made available to scientists for analysis and manipulation. While database management systems (DBMSs) provide the capabilities required for storing, accessing, and manipulating data, they have no facilities to support the appropriate, application-specific level of abstraction expected by scientists. Consequently, a data management system for a scientific application usually involves (1) mechanisms for defining the application-specific data structure and operations (e.g., in terms of maps, images, and experiments); (2) a database implemented by using a DBMS containing the application data and providing various capabilities for managing these data; and (3) mappings between the structure and operations of the application-specific data and the structure and operations of the DBMS-specific database.

The researchers' database tools are aimed at (1) increasing the productivity, efficiency, and accuracy of developing data management systems for scientific applications and (2) increasing the adaptability of such systems to structural changes of the underlying application. The database tools fulfill these aims by providing automatic translation of the application-specific data structure and operations into DBMS-specific database structure and operations. The database tools insulate users from the underlying DBMS, permitting them to interact with the data management system in terms of their specific application rather than in terms of the underlying DBMS.

Scientific application should share and exchange data. Data management systems for different applications are characterized by various degrees of heterogeneity; such systems are usually based on different DBMSs and reflect different conceptual views of the applications. For such heterogeneous data management systems, tools for facilitating data sharing and exchange are being developed. (RPIS 4981(H))

279. Laboratory Information Management System for Megabase Sequencing

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\$184,000

A laboratory information management system (LIMS) is an electronic version of a molecular biology laboratory notebook. The LIMS is intended to support a variety of sequencing protocols and be readily adaptable as protocols are modified. LIMS is flexible and reusable, easily adaptable to a variety of protocols, and easy to query, modify, and maintain so that it is useful to a wide variety of molecular biology laboratories, including genome centers and other DNA sequencing labs. The main goal of LIMS is to permit users to interact with the system in terms of graphical descriptions of biological protocols. This LIMS supports specifying the structure of protocols as well as querying the system in terms of protocols and objects. The system is easy to use, manage, understand, and adapt to because users may interact with it in terms of their own frame(s) of reference.

A graphical protocol editor, which permits biologists to specify new protocols by graphically constructing a protocol process flow diagram, and protocol browsing and querying facilities, which allow biologists to browse protocol specifications and to specify queries in terms of protocols, are being developed. The protocol specification is hierarchical, so that the protocol designer can progressively specify the protocol in increasing levels of detail. The process flow diagrams are mapped automatically into Extended Entity-Relationship (EER) schemas then into relational database schema definitions. Protocol queries are mapped automatically into EER-based queries and then into relational database queries. The database tools already developed by these researchers are used to generate schema definitions from EER schemas and to generate database queries from EER queries. The Caltech co-Principal Investigator coordinates the collaboration with the National Science Foundation Center for Molecular Biotechnology directed by Dr. Hood and provides the interface to the actual process of large scale sequencing. (RPIS 5610)

280. Human Genome Center/Information Management System

J.L. McCarthy
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This task provides computer databases and user interfaces for collaborative development of genomic map, sequence, and image data by Lawrence Berkeley Laboratory's (LBL's) Human Genome Center researchers. As data are being developed, such project-level computer groupware helps research scientists manage and present candidate information that is not yet ready for public distribution. Such software lies logically between instrumentation and laboratory information management for experimental data acquisition, on the one hand, and public repository databases for archiving final results, on the other.

The overall goal is seamless integration of data, diagrams, and digital images with other components of the biologist's computing environment. The approach is to use high level tools for design of user interfaces and databases, along with commercial software for implementation of databases and user interfaces. Modular design and separation of user interfaces from underlying data management systems facilitates independent development and evolution of different software modules within an integrated framework. Commercial and research software from external sources are being used wherever possible to build on the work of, and collaborate with, others who are addressing similar problems.

Another important feature of this modular approach is to provide an evolutionary path to meet changing database and interface needs of LBL's Human Genome Center researchers as technology in both biology and computer science evolves. To address immediate needs as well as to define longer term user requirements, researchers have begun by helping LBL biologist use simple, single-user software tools (such as spreadsheet and file management programs) to define, enter, and manage their initial data in formats that can later be uploaded to shared community databases as those become operational. At the same time, community databases and interfaces that can be used by multiple users running on different types of workstations to manage and access different types of images, diagrams, text, and tabular data are being developed. (RPIS 4981(1))

281. Human Genome Center/Algorithms for Mapping and Sequencing the Human Genome

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A mathematical biology research program that will encompass both computational biology and statistics is being initiated at Lawrence Berkeley Laboratory. Researchers are creating and analyzing efficient combinatorial algorithms, statistical procedures, and prototype software for (1) physical mapping (i.e., ordering clone libraries) and (2) assembly of DNA sequence fragments from overlapping random clones into contiguous sequences.

Assembling the physical map and sequence of the human genome from experimental data is impeded by slow computations and by software that does not adequately cope with common errors in experimental data. Researchers will address these problems by creating combinatorial algorithms that are both substantially more efficient and more resilient to experimental errors. The problems to be addressed (ordering clone libraries, shotgun sequence assembly) are central to the most widely used strategies for mapping and sequencing the human genome.

In physical mapping, researchers are dealing with false positive overlaps and chimeric clones. In shotgun sequence assembly, researchers are dealing with repetitive DNA sequences during sequence assembly. A SEMIGREEDY shotgun sequence assembly algorithm that promises to be substantially faster than conventional algorithms, as well as amenable to use with directed closure strategies, is also being investigated.

The project involves the development of both sequential and parallel algorithms. The project is a collaboration of biologists, computer scientists, and statisticians and would expand current efforts supported by the DOE-OHER Human Genome Office at the University of California, Berkeley (UC Berkeley) and the University of California, Davis (UC Davis).

The research program will be closely integrated with ongoing graduate training programs in computational biology and statistics at UC Berkeley, UC Davis, and the California Institute of Technology. (RPIS 4981(J))

282. Human Genome Center/Software and Data Resource Facility

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Development of new software is expensive in terms of time and personnel; such development is warranted only when the available programs do not meet or fully satisfy the needs of the project. Data analysis in the genome project is an integral part of the effort and can benefit from developments in computational biology as well as from the use of information compiled in public databases. The Software and Data Resources Facility will maintain onsite all relevant databases with molecular biology information, facilitate access to public services, and integrate public and local resources. In the facility it provides public domain and commercial software for the Human Genome Center and collaborates with outside researchers to foster software development. To benefit a larger community, the databases and software installed at Lawrence Berkeley Laboratory (LBL) is distributed to two other laboratories: the University of California, Berkeley, Department of Molecular and Cell Biology and the Human Genome Center at Lawrence Livermore National Laboratory. This export uses standard Unix tools and poses no additional cost to LBL. To improve access to the information for genome researchers, an effort to integrate and customize the imported software and database interfaces is being undertaken to make the best use of available resources. This development will mutually benefit the project on database tools at LBL. (RPIS 4891(O))

Life Sciences Division

283. Human Genome Center/High Resolution Genetic Mapping

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This task develops and implements technologies aimed at high resolution mapping of individual human chromosomes. Initial efforts have focused on developing strategies that lead to identification and characterization of polymorphic microsatellite repeat sequences. Microsatellite repeats are extremely abundant in all mammalian genomes and usually have multiple, highly informative alleles. A method for making derivative genomic libraries, 40–50 percent of whose members contain microsatellite repeats, has been developed. Researchers intend to construct high density

genetic maps of a single chromosome with polymorphic repeat markers spaced every 0.5–1.0 cMorgans.

Strategies that are amenable to robotics and multiplex analysis and that can be used to follow the segregation of alleles through genetic crosses are also being developed. Researchers are exploiting the biological properties of the *Escherichia coli* MutS protein to develop an assay system for determining whether an individual is a homozygote or heterozygote at a particular locus. Using polymerase chain reaction-based markers and a 96-well enzyme-linked immunosorbent assay format, researchers can obtain information about the segregation of alleles for hundreds of loci in a matter of hours. (RPIS 4981(K))

284. Human Genome Center/Distribution of DNA Sequences as Signals of Origin

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Yeast artificial chromosomes (YACs) are an efficient way to provide first coverage of large regions of contiguous DNA. Many of the human YAC clones in existing libraries contain unrelated pieces of DNA. A series of experiments is being undertaken to determine the origin of the artifactual clones and related issues on the stability and growth characteristics of the artificial chromosomes. Central to these experiments is the cloning of DNA fragments representing defined regions rather than random segments of the genome. The possibility of assembling large contigs from the defined fragments is being examined. The use of defined fragments depends on the distribution of the short DNA sequences used to cleave the genomic DNA. Computer studies on the distribution of oligonucleotides in the genome are being initiated. For these computational analyses, researchers are developing new tools that rapidly analyze 10-megabase DNA sequences, which will derive from sequencing of model genomes and pilot studies on the human genome. The computer studies will also help in the design of large numbers of DNA primers for the polymerase chain reactions used in many parts of the genome project. (RPIS 4981(N))

Lawrence Livermore National Laboratory Livermore, CA 94550

Human Genome Center

285. Human Genome Center

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The Human Genome Center at Lawrence Livermore National Laboratory is a multidisciplinary team effort. The broad goals of this effort are to develop biological and physical resources useful for genome research, model and evaluate DNA mapping and sequencing strategies, couple these resources and strategies in an optimal way to construct ordered clone maps and DNA sequences of human chromosomes, and use the map and se-

quence information to study genome organization and variation. The first of three areas of research is the Core Facility, which provides general support to Center projects that include cell culture and DNA extraction; library, probe, and clone management; routine synthesis of oligonucleotides; and administration. The focus of Physical Mapping is the assembly, closure, and characterization of contig maps; the linkage of the physical map to the genetic map; the localization and orientation of contigs by fluorescence in situ hybridization; the isolation, mapping, and characterization of coding regions; and the development of new methods for mapping. Enabling Technologies develop and provide resources useful to many components of the Center. The computational effort is responsible for the mathematical modeling of mapping strategies, the development of data analysis algorithms, data processing, and the construction and maintenance of interactive relational databases for internal and external access. This effort has led to the development of a generalized software tool for the graphical visualization and manipulation of map data. The instrumentation effort is developing new flow systems technology for high resolution chromosome analysis and purification as well as image analysis systems to assist in fluorescence in situ hybridization. (RPIS 4835 (A-I))

286. Computational Support for the Human Genome Center: Statistical and Mathematical Analysis, Data Processing, and Databasing

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This project provides mathematical and computational support for the genomic mapping efforts underway at Livermore. The researchers' primary goals were the development of a fully computer-automated technology capable of turning raw restriction fingerprint data into an assembled contig map, the quality of which exceeds (at a minimum) that achievable by manual data analysis methods; the implementation of a fully integrated, high quality database system (1) in which all relevant experimental and derived data (along with associated laboratory notebook data) are stored and (2) that supports both standard query interfaces and network access; and the development of an interactive visual interface to all data that (1) is maximally useful and informative, (2) provides for integrated map constructs, (3) uses standard graphical, open systems, and windowing environments, and (4) is fully integrated with the total project database system. Significant effort on these three goals continues, but the bulk of the work on them is completed. Researchers are presently emphasizing the development of analytical, database, and data visualization tools for assembling, managing, and statistically characterizing integrated maps; the development and testing of systems both for direct access by remote users and for automatic bulk data export to centralized databases based on direct network access to the Center's database through a programmable client-server interface; and the evaluation of (1) mapping progress, (2) the

efficiency and accuracy of the contig building strategy, and (in part through internal collaboration) (3) the biological and analytical reasons for deviations between theoretical expectations and actual results, and researchers are also supporting, and collaborating on, efforts to develop tools for managing, processing, and analyzing sequence data (e.g., sequence contig assembly and homology searches). (RPIS 4835(A))

287. Core Facility

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The Human Genome Center consists of several projects that use many of the same DNA reagents and techniques. A genome center scientific core facility was established to provide the cloned DNAs, synthetic DNA oligomers, and routine DNA sequencing support needed by the various projects in the chromosome 19 mapping effort. The functions of the core facility are to maintain and screen the arrayed cosmid and yeast artificial chromosome libraries, isolate individual cosmid DNAs for use in fingerprinting and hybridization procedures, prepare colony and DNA filters for hybridization, maintain the collection of known probes for chromosome 19, isolate DNA from cultured mammalian cells, and synthesize DNA oligomers.

During the past three years, the facility has arrayed and completed the screening of two chromosome 19 cosmid libraries in three different hosts (30,000 clones total), isolated DNA from more than 12,000 human-specific clones, collected more than 120 probes for known chromosome 19 genes and loci, and synthesized more than 1,200 DNA oligomers for use as primers and hybridization probes for polymerase chain reactions and sequencing. The concentration of these tasks in a central core facility ensures the proper management and quality control of these valuable resources being generated by the various projects and minimizes duplication of effort by different investigators requiring the same materials and services. In addition, this project provides the administrative support for the Center and for the individual scientific staff. (RPIS 4835(B))

288. New Mapping Strategies

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The main focus of this subproject is to design, test, and optimize novel procedures for mapping the human genome, in particular those tailored to the closure of the chromosome 19 map and those important for the physical mapping of chromosome 2. A technology that has been developed is inter-*Alu*-polymerase chain reaction (PCR), which is used to amplify probe sequences or to generate distinctive PCR fragments for fingerprinting. *Alu*-PCR products can reproducibly be generated from hybrid cells, from DNA fragments in pulsed-field gels, and from different types of large-insert recombinant

clones (e.g., cosmids or yeast artificial chromosomes [YACs]). The *Alu*-PCR products from the various hybrids or from microdissected chromosome segments can be used to assign cosmids and YACs to chromosome regions. Such cosmids and YACs can serve as the seed clones for closure through high throughput chromosome walking procedures. Several new approaches to facilitate the closure of chromosome 19 are being developed and tested. These include explorations to increase the efficiency of chromosome-walking procedures, based on the use of either probe or target pooling approaches; creation of chromosome-specific subsets from genomic YAC libraries to permit working with clones reduced about fiftyfold in number; and use of the reduced-complexity YAC array to link cosmid contigs.

Special attention is being given to procedures that reduce the complexity of the chromosome 2 mapping problem through the use of bacterial clones with inserts larger than cosmids and through the creation of chromosome- and/or region-specific subgroups of these clones. In addition, the high risk, high payoff options offered by the *RecA* Achilles-Heel cleavage procedure (Koob and Szybalski, 1991 and Ferrin and Camerini-Otero, 1991) will be explored so that map distances can be estimated by pulsed-field electrophoresis and region-specific large fragment libraries can be established. (RPIS 4835(C))

289. National Laboratory Gene Library Project

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The goal of the National Laboratory Gene Library Project is the production of chromosome-specific human gene libraries and their distribution to the scientific community for studies of the molecular biology of genes and chromosomes, for the study and diagnosis of genetic disease, and for the physical mapping (ordering) of chromosomes. Phase I—the production of complete digest libraries from each of the human chromosomal types purified by flow sorting—has been accomplished. Phase II—the construction of libraries with large inserts in lambda replacement vectors and in cosmid vectors—is now approaching completion. Such large-insert libraries are better suited than Phase I libraries to studies of gene structure and function, organization of genes on chromosomes, and ordering of cloned sequences.

Most libraries have purities in the range of 80–95 percent. Researchers intend to reconstruct the few lower purity libraries from better batches of sorted chromosomes.

Researchers are also exploring the use of more advanced chromosome-specific libraries, using vectors with improved stability of insert size. Furthermore, they are collaborating with two external groups to optimize large-insert cloning in F-plasmid vectors or P1-derived vectors. If the construction of such libraries appears feasible, more libraries will be prepared for eight limited sets of chromosomes. Efforts to construct custom libraries for selected chromosomes are being intensified, using improved technologies. (RPIS 4835(D))

290. Coding Region Isolation, Mapping, and Characterization

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This effort isolates, sequences, and maps coding regions that are either located on specific human chromosomes or of significant interest to the biomedical community. In the form of cDNAs or genomic exons, these regions will integrate the developing clone-based physical maps with relevant genetic information. This subproject involves six main components. First, randomly selected cDNAs derived from human tissues are being partially sequenced and compared against existing sequence databases for interesting homologies. Second, cDNAs selected by various means as candidates for chromosome 2 or chromosome 19 genes are being isolated, sequenced, and mapped (along with the randomly selected cDNAs). The techniques to enrich for chromosome-specific cDNAs include the screening of cDNA library arrays with chromosome-specific cosmids, with probes derived from syntenic regions of other species (e.g., mouse) and by hybrid selection or exon amplification. Third, partial sequences from genomic regions of chromosome 19 are being collected. Initially, these form a basis for sequence-tagged site selection and polymorphic marker selection. As a step toward obtaining the sequence of chromosome 19, the sequences are also being scanned for their potential as coding sequences, and corresponding cDNAs are being isolated for correctly predicted exonic regions. Fourth, as the need for high throughput mapping of cDNAs to chromosomes and subchromosomal regions increases, researchers are developing, in collaboration with the instrumentation group, techniques that promise to rapidly and simultaneously map cDNAs. The fifth main research component consists of the use and analysis of large arrays of cDNA clones in studies of gene expression and variation as well as to classify cDNA clones into gene families. Given the interest of the genome communities in having the full-length versions of cDNAs from many genes, the sixth main research component of this effort is work on techniques to identify and create full-length cDNAs; researchers will be collaborating with other groups within the Biomedical Sciences Division on cloning cDNAs of particular interest. (RPIS 4835(E))

291. Interdigitation of the Physical and Genetic Maps of Human Chromosome 19

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The goal of this project is the interdigitation of the physical/contig map and the genetic/expression map of human chromosome 19. The goal involves three efforts: (1) identification of cosmids containing genetic markers to serve as "anchors" for the physical map, (2) assignment of selected cDNAs mapping to chromosome

19 to cosmids, and (3) generation of sequence-tagged sites (STSs) within mapped cosmids. "Anchor" cosmids have been identified for >90 genes and 20 anonymous markers. The "anchor" point effort will continue with the ~40 remaining, currently available, mapped genes and probes. Obviously, new probes and markers will continue to be mapped to chromosome 19 and need to be placed on the contig map. The isolation of cDNAs is also a significant focus of the Center effort. Mapping of these cDNAs to specific cosmids will provide material for further analysis, including sequencing and studies of gene function. The cDNA sequence will be used to establish expressed sequence tags. The genetic map will be completed by generation of STSs as well as a limited number of polymorphic markers from specific cosmids. Currently, STSs have been generated for 12 of the original 13 reference polymorphic loci. In summary, the foremost application of the cosmid overlap map will occur in the search for functionally significant loci, including disease genes. The genetic markers will be the landmarks that define a set of ordered cosmids containing any locus of interest on chromosome 19, therefore the necessity for parity of the maps. (RPIS 4835(F))

292. Assembly, Closure, and Characterization of a Chromosome 19 Contig Map

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The chromosome 19 physical map being established at Livermore consists of a foundation of cosmid contigs established by automated restriction fragment fingerprint analysis. This foundation is now represented in 871 contigs, 165 of which have been regionally localized on the chromosome by fluorescence in situ hybridization. The total minimum spanning path consists of 3,057 cosmids, constituting an estimated 75–80 percent of the chromosome. A major effort is now being made to close the gaps between these contigs, initially using yeast artificial chromosomes (YACs) as linking agents. Probes from regionally localized contigs and genetic markers are being used to screen YAC libraries and identify YACs spanning a limited region. Cosmids corresponding to these YACs are being identified by hybridization of probes derived from the YACs onto high density cosmid colony arrays. To obtain clonal continuity where possible at the cosmid level, probes made from the ends of these localized contigs are being hybridized to the cosmid library to identify cosmids likely to extend the contigs. To increase efficiency, hybridizations are being performed in a multiplex fashion. Distances along the map and the ordering of contigs will be achieved by fluorescence in situ hybridization. Areas of particular interest identified in the process of contig construction—such as disease gene loci, gene families, and repetitive elements—will be analyzed more extensively to reveal more about detailed gene structure at these loci. This in-depth analysis will also confirm the validity of contigs established by the fingerprinting and walking procedures. (RPIS 4835(G))

293. DNA Sequence Mapping by Fluorescence In Situ Hybridization

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Fluorescence in situ hybridization (FISH) has four main roles in the construction of a long range map of chromosome 19: (1) localizing cosmids to chromosomal bands, (2) checking contig construction, (3) identifying cosmids distributed at approximately 3-Mbp density along the chromosome, (4) ordering cosmids within these 3-Mbp intervals, and (5) estimating the distance between cosmids. Cosmids are nonradioactively labeled with biotin or digoxigenin. Probe hybridization sites are labeled with fluorescent tags (e.g., Texas Red or FITC [green]), which can be viewed simultaneously. By using a combination of targets of increasing decondensation (metaphase, somatic interphase, and pronuclei formed after fusion of eggs and sperm), sequences separated by 50 or more kbp can be ordered. Researchers have regionally localized 456 cosmids to cytogenetic bands on chromosome 19. Of the mapped cosmids, 367 have been assembled with other chromosome 19 cosmids into a total of 165 contigs by automated restriction enzyme fingerprinting. FISH has been used to confirm the assembly of 97 of these contigs by testing that members of the same contig map to the same location in metaphase chromosomes. Two-color fluorescence in situ hybridization has been used to develop a high resolution map using 62 cosmids. These cosmids were ordered relative to each other on metaphase chromosomes. Such metaphase mapping allowed the 62 cosmids to be ordered into 31 intervals. A more refined order was established by iteratively determining the order of three probes simultaneously hybridized to interphase nuclei. With the added information from interphase mapping, the 62 cosmids could be ordered into 57 distinct intervals, at an average density of one marker per 1.1 Mbp. Hybridization to highly decondensed chromatin in human sperm pronuclei after fusion with hamster eggs was used to order nine carcinoembryonic antigen-family genes within a 1.2-Mbp region of 19q13.2. (RPIS 4835(H))

294. Instrumentation for Cytogenetics and Gene Mapping

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This program is developing instruments that support the Human Genome effort at Livermore. Instruments for karyotype analysis, chromosome sorting, fluorescence in situ hybridization, and the mapping of probes and cDNAs to chromosomes are being developed. A specially designed modular flow cytometer is being used for both high resolution karyotype analysis and high speed chromosome sorting. The design of the flow sorter has been licensed to industry. The sorting capabilities are being extended to six-way sorting for probe mapping. Two methods for evaluating fluorescence in situ hybridization experiments are under development. Microscopic images on film are

processed with a digitizer-board-based system. For the collection of low intensity fluorescent images, a new CCD-camera-based microscope workstation is being built. The software that operates the flow sorters and the image analysis instruments are being transferred to UNIX-based computers to facilitate the exchange of data between the acquisition programs and standard data analysis and text manipulation programs. (RPIS 4835(I))

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Center for Human Genome Studies

295. Center for Human Genome Studies

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\$7,746,000

The Los Alamos Center for Human Genome Studies provides coordination, technical oversight, and direction for the following interdisciplinary elements of the Human Genome Program at Los Alamos: physical mapping, new technology development, and informatics. The center also develops collaborative research and development programs with the private sector and with other centers for human genome research.

The goals of this project are to (1) develop concepts and advance technology for genomic physical mapping and (2) construct a contig physical map of human chromosome 16 that includes an ordered set of overlapping DNA fragments encompassing the chromosome. Such a map will consist of DNA clones with 1-2 Mb of connectivity, covering more than 95 percent of the eukaryotic arms of this chromosome (90 Mb), with evenly spaced sequence-tagged site (STS) markers (*The U.S. Human Genome Project: The First Five Years, FY 1991-1995, DOE/ER-0452P*). The physical map will integrate cosmid and yeast artificial chromosomes (YAC) contigs with the genetic linkage map, identified gene sequences, and the cytogenetic map into a tool that allows rapid access to any region of chromosome 16 for analysis and eventual large scale sequencing. The first phase of this project has been achieved, with the ordering of large "nucleation" cosmid contigs (>100 kb) covering approximately 60 percent of chromosome 16. Map closure is now underway, using chromosome 16 YACs from total genomic and flow-sorted DNA libraries. In pilot studies, the direct generation of STS markers from DNA obtained from flow-sorted human chromosomes has been achieved, as has the generation of nonchimeric, chromosome-specific YAC libraries. These capabilities allow the expansion of activities to encompass the physical mapping of other human chromosomes. Priority is being placed on a low resolution map of human chromosome 5. The significance of this work lies in the immediate application of this knowledge to (1) understand human genetic disease, (2) clarify the molecular bases for genetic disease susceptibility, especially in regard to energy-related chemical or radiation exposures, and (3) reveal the molecular details underlying long range chromosome architecture and dynamics. (RPIS 5063(A-L))

296. Pooling Yeast Artificial Chromosome Libraries for Screening with Unique Sequences

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Efficiently accessing libraries of cloned DNA and clones in physical maps is a technical challenge with far-reaching ramifications for mapping and sequencing.

T-designs (Beth, T., et al. [1986] *Design Theory*, Cambridge Univ. Press) have been found to be optimal in that they enable one to locate all clones in a library containing a unique sequence via a minimal number of polymerase chain reactions (PCR) and pools. The t-design pools include subsets of the clones not constrained to lie in rows, columns, or plates, and they have the advantage of allowing redundancy for correcting false-negative or other erroneous PCR results.

The t-designs are applied to the pooling of several yeast artificial chromosome (YAC) libraries created at Los Alamos National Laboratory. One of these pooling schemes is similar to those proposed by Barillot et al. and deJong; these have the property of being nearly as efficient as t-designs and they can be easier to construct.

Novel pooling schemes, not necessarily involving t-designs, are optimal when the number of library screenings becomes sufficiently large and when the number of positive clones expected per screening is 6 or greater. Pooling schemes for this case are also described, where it is appropriate to pool both the library and the unique sequences that one wishes to screen the library with.

Robots are being programmed to make the aforementioned pools for each of several YAC libraries consisting of 500-40,000 clones, for the purpose of screening for unique sequences. The programming of the Beckman and Packard robots will be described. (RPIS 5063(B))

297. Construction of a 1.6 Megabase Average Resolution Sequence-Tagged Site Map of Human Chromosome 16

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This project is constructing a detailed cosmid yeast artificial chromosome (YAC) and sequence-tagged site (STS) physical map of human chromosome 16. This map currently consists of 4032 fingerprinted cosmid clones and 334 YAC clones (hybridized to high density arrays of cosmid clones) which make up 462 islands of 218 kb average size and cover 94 percent of this

chromosome. Regional localization of these islands is accomplished by multiplex polymerase chain reaction deletion analysis of sequence-tagged sites in somatic cell hybrids. The hybrid panel contains 50 breakpoints with an average resolution of 1.6 megabases. STSs are developed from the end clones of cosmid contigs. To date, 408 cosmid end clones have been sequenced, and more than 100 STSs have been developed and localized to the hybrid breakpoint panel, resulting in a 1.6 Mb average resolution STS map of chromosome 16. Gene Recognition and Analysis Internet Link analysis indicates that 14 percent of the 408 cosmid sequences may contain open reading frames. One sequence has high similarity to inosine monophosphate dehydrogenase, suggesting that it may be a third locus for this gene family. (RPIS 5063(C))

298. Human Recombinant DNA Library

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\$1,462,000

The National Laboratory Gene Library Project is producing chromosome-specific human gene libraries and distributing them to the scientific community for (1) studies of the molecular biology of genes and chromosomes, (2) study and diagnosis of genetic disease, and (3) physical mapping of chromosomes. This is a cooperative project using the flow-sorting and molecular-cloning expertise at Los Alamos National Laboratory (LANL) and Lawrence Livermore National Laboratory (LLNL).

The specific aim of the project's first phase was the production of complete digest libraries from each of the human chromosomal types purified by flow sorting; the average insert size expected was about 4 kb. The bacteriophage lambda vector used was Charon 21A, which has both EcoR I and Hind III insertion sites accommodating human DNA fragments of 0–9.1 kb. Each laboratory produced a complete set of chromosome-specific libraries—LANL with EcoR I and LLNL with Hind III. The small-insert libraries are deposited in the American Type Culture Collection, Rockville, Maryland; more than 3,200 aliquots representing more than 600 chromosomes-specific libraries have been distributed to more than 750 laboratories worldwide.

The second phase of the project involves construction of partial-digest libraries with larger inserts in more advanced, recently developed lambda vectors (9–23 kb) and in cosmid vectors (33–46 kb). These large-insert libraries have characteristics that are better suited to basic studies of gene structure and function, organization of genes on chromosomes, and ordering of cloned sequences. The second-phase strategy is to divide responsibility for the genome between the two laboratories, with LLNL cloning chromosomes 1, 2, 3, 7, 9, 12, 18, 19, 21, 22, and Y and LANL cloning chromosomes 4, 5, 6, 8, 10, 11, 13, 14, 15, 16, 17, 20, and X. In this way, each chromosomal type will be cloned into both lambda and cosmid vectors. Cosmid libraries have been constructed and arrayed in microtiter plates

at LANL for chromosomes 5, 6, 8, 11, 13, 16, and 17 in Charon 40 and λ Cos1. Libraries have also been constructed in M13 or bluescript vectors for chromosomes 5, 7 and 14. They provide a rich source of sequence-tagged site markers for the insert selection for specific chromosomes in genomic yeast artificial chromosome (YAC) libraries. A library for chromosome 21 has also been constructed in the YAC vectors pJS97 and pHS98. (RPIS 4408)

299. Construction of a Cosmid, Yeast Artificial Chromosome, and Sequence-Tagged Site Physical Map of Human Chromosome 16

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This project is constructing a detailed physical map of human chromosome 16. This map was generated by the fingerprinting of 4032 chromosome 16 cosmid clones and the hybridization of 411 chromosome 16 yeast artificial chromosome (YAC) clones (both constructed from flow sorted chromosomes) to high density membrane grids of these cosmids. The map is comprised of 462 islands having an average size of 218 kb. The coverage of the chromosome in these contigs is 94 percent. Islands have been regionally localized to a somatic cell hybrid breakpoint map using sequence-tagged sites (STSs) derived from the end clones of cosmid contigs. A total of 140 island (cosmids and YACs) and singleton cosmids covering ~24 Mb or 25 percent of chromosome 16 has been regionally localized on the chromosome. The somatic cell hybrid panel consists of 54 different hybrids that produce a cytogenetic-based physical map with an average resolution of 1.6 Mb. A 1.6 Mb average resolution STSs map has been developed from contigs mapping to each region of this cytogenetic map. More than 50 known genes and markers have been integrated into the map by fingerprinting of cosmid clones and hybridization of probes to the high density cosmid membranes. This map is facilitating the cloning of various disease loci and fragile sites on chromosome 16. (RPIS 5063(D))

300. Sequencing and Mapping of cDNAs from a Paternally Encoded Human Pregnancy

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This project is examining gene expression in an unusual human pregnancy (hydatidiform mole) by cDNA library construction and cDNA sequencing. This pregnancy is exclusively of paternal genetic origin and results from paternal genetic imprinting. This project will determine if the genes expressed uniquely in hydatidiform mole are encoded for by a subset of sperm chromatin that hypothetically may be involved in paternal imprinting.

Complete hydatidiform moles are abnormal diploid pregnancies that result from the fertilization of an enucleated ovum. The pregnancies are characterized by hypertrophy of the trophoblast, hydropic degeneration of all placental villi, absence of a fetus, and a propensity to become malignant. The mole has maternal mitochondria DNA but paternal chromosomes. Diploidy is restored by either fertilization by two sperm, or in the majority of cases fertilization by one sperm, which undergoes duplication without cytokinesis.

An analysis of more than 1,200 cDNA clones from a directionally cloned and arrayed nonamplified cDNA indicates that approximately 10 percent are homologous to known DNA sequences, 10 percent contain repetitive elements, less than 1 percent lack inserts, and the remainder represent newly identified genes. Of the newly identified genes, approximately 40 percent contain regions of limited homology that may indicate function. The homologous sequences also provide information on tissue-specific RNA splicing.

In collaboration with another investigator, chromosomal localization of cDNA clones using fluorescence in situ hybridization (FISH) has been initiated. This approach has successfully been used to map single copy genes with high fidelity. Sequence-tagged sites (STSs) are generated for the cDNAs that are mapped using FISH. The STS primers are then used to determine the organization of the gene in human sperm chromatin by a polymerase chain reaction-based assay. Using this assay, cDNAs have been localized to distinct sperm chromatin components. (RPIS 5063(E))

301. Systematic Generation of Chromosome 5 Specific Sequence-Tagged Sites

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The systematic generation of chromosome 5 specific sequence-tagged sites (STSs) is in progress, utilizing flow-sorted human chromosomes. Chromosomes were purified from either normal cells or a monochromosomal cell line. Purity estimates of approximately 95 percent were obtained, yielding a 50-fold enrichment. DNA from approximately 200,000 chromosomes was digested with two restriction enzymes (usually *Bam*HI and *Hind* III) and cloned directly into the bacteriophage M13 mp18. One pass sequencing was conducted with a Dupont Genesis 2000 automated sequencer. Approximately 15 percent of the greater than 500 random DNA sequences analyzed contain putative coding regions, as determined by DNA homology searches, or Gene Recognition and Analysis Internet Link analysis (Oak Ridge National Laboratory). Following further analysis to identify common human repetitive sequences, appropriate polymerase chain reaction (PCR) oligomers were synthesized in unique regions. An acceptable STS-PCR assay yielded the appropriate size amplification product from hybrid cell line DNA containing only human chromosome 5. Eleven cell hybrids that retain chromosome 5 from individuals with deletions or translocations of the long arm have been isolated. These 11 hybrids, along with 12 hybrids with deletions of 5p, represent a natural deletion mapping panel that defines 30 discrete segments of chromosome 5. To date, more than 100 of the chromosome 5 STSs have been regionally ordered using this mapping panel. The STS markers appear to be randomly distributed along the length of chromosome 5. The exact order of a subset of STSs was determined by the use of radiation hybrid panels of chromosome 5. These results demonstrate that a 0.5-1 Mb STS map of chromosome 5 is achievable using these approaches. (RPIS 5063(F))

302. Rapid DNA Sequencing Based on Fluorescence Detection of Single Molecules

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\$1,100,000

A laser-based technique for sequencing 40-kb DNA fragments at rates up to several hundred bases per second is being developed. This approach relies on fluorescent labeling of all the bases in a single DNA fragment, attaching the labeled fragment to a support, moving it into a flowing sample stream, and

detecting the individual labeled bases as they are cleaved from the DNA fragment by an exonuclease. The ability to sequence such large DNA fragments will reduce significantly the subcloning and sequence assembly steps now required to acquire megabase segments of sequence information.

Significant progress has been made in the detection of individual molecules. Time-resolved photon counting in a system using a mode-locked, frequency-doubled Nd:YAG laser has demonstrated the ability to detect individual Rhodamine-6G molecules as they pass through the laser beam. Individual molecules of Rhodamine-6G and Texas Red are now being detected simultaneously in a two-color experiment. Detailed studies of the photophysics of fluorescent molecule decomposition are underway to determine the conditions under which a molecule will emit the maximum number of photons. In addition, techniques to determine the fluorescence lifetimes of individual molecules are being developed.

Flow-cytometric sorting techniques are being used to identify and separate microspheres attached to individual lambda-phage DNA molecules. The microspheres will be manipulated and suspended by using a microinjection pipette or a laser-based optical trap.

The synthesis of a completely labeled DNA strand is necessary for the technique to work. Studies to determine the limits of labeling with several compounds are underway. Initial efforts used commercially available biotinylated nucleotide precursors as the first model compounds for incorporation into the synthesized second strand. The complete replication of an M13 phage with all its incorporated cytosine and thymidine bases tagged with biotin has been achieved. The replication of M13 is now being investigated using fluorescently labeled nucleotides. Replication out to 3 or 4 kb with 1 labeled base and out to about 500 bases with 2 labeled bases has been demonstrated. Modifications in the structure of the linker arm connecting the fluorescent dye to the nucleic acid are expected to improve the replication results.

A Cooperative Research and Development Agreement has been signed with Life Technologies, Inc., (LTI) of Rockville, Maryland. LTI will be responsible for the nucleic acid chemistry and enzymology associated with this project. The principal investigator for the LTI effort is J.D. Harding, P.O. Box 6009, Gaithersburg, Maryland 20877 (301) 670-7649. (RPIS 4865)

303. Genetic Analysis of Yeast Artificial Chromosome Following Yeast Transformation and Mitotic Growth

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It is essential for the accurate characterization of the genome that the DNA within yeast artificial chromosomes (YACs) be an exact replica of that in human cells, that there be no cloning artifacts, and that the YACs remain stable within yeast. However, present YAC cloning systems produce several types of cloning errors, including cocloned DNA sequences (chimeras of DNA from different regions of the genome), rearrangements during transformation, and instabilities during growth. This project developed genetic systems that can signal physical changes in YACs. In these studies, a cassette *Alu-HIS3-Alu* has been targeted to YAC12 which contains 360 kb from chromosome 21. These model YACs (*telomere TRP1-HIS3-CEN URA3 telomere*) were examined for loss of the *HIS3* marker during transformation and subsequent mitotic growth. The frequency of internal deletions in mitotically growing cells was approximately 10^{-4} to 10^{-5} . Physical analysis of 30 *his3⁺ TRP1⁺ URA3⁺* colonies revealed the replacement of the 360 kb parental YAC by a smaller YAC, 50 to 310 kb in size. The new YACs contained the original telomeres. A likely source of deletions is recombination between repeats such as *Alu*'s. These results are in sharp contrast to those obtained with YACs undergoing transformation. Nearly 30 percent of the transformed YACs lacked the *HIS3* marker. The transformation-associated loss was also due to deletion, with the size varying between 50 and 180 kb. As expected, a high frequency of deletions was observed even in YACs retaining the *HIS3* marker; 10 percent of the *HIS⁺* YACs exhibited deletions in the range of 50-100 kb. Similar results were obtained with another YAC containing a 360 kb insert of mouse DNA. Possible sources of the unexpectedly high level of transformation-associated rearrangement include methods of YAC isolation/preparation and transformation. Regardless of the reasons, the high level was subject to *RAD52* control. The *RAD52* mutant exhibited a greater than 10- to 20-fold lower level of human YAC instability during transformation as well as during mitotic growth as compared to an isogenic *RAD⁺* strain. These results demonstrate that YAC instability can be genetically characterized. This project is pursuing the genetic control of YAC instability to improve the system for YAC cloning. (RPIS 5063(G))

304. High Precision Mapping of Yeast Artificial Chromosome Clones onto Chromosome 21 by Fluorescence In Situ Hybridization and Image Analysis

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Yeast artificial chromosome (YAC) clones containing human chromosome 21 DNA inserts (100-400 kb, 200 kb average) from flow-sorted chromosomes have been mapped onto human diploid fibroblast metaphase chromosomes by fluorescence in situ hybridization (FISH) and digital imaging microscopy. This mapping seeks to (1) provide a complete long-range physical map of chromosome 21 with 1-Mb resolution between YACs and (2) provide subregional location and ordering of known and unknown markers on the long arm of chromosome 21, particularly in the Down's syndrome region (q22). Mapping of the fluorescent DNA probe to its location on the chromosome in a metaphase spread is done using a procedure modified from Lichter et al. YAC clones are indirectly labeled with fluorescein and the total DNA of the chromosome is counterstained with propidium iodide. Through the use of a 520-nm-long pass emission filter, both the FISH signal and the whole chromosome can be viewed together. One image is acquired for each chromosome of interest containing the fluorescent probe signal in a metaphase spread. From the digitized image, the fluorescence intensity profile through the long axis of the chromosome gives the total chromosome length and the probe position. The map position of the probe is expressed as the fractional length (FL) of the total chromosome relative to a fixed reference point that is designated FL_{pter}. From each hybridization, 20-40 chromosomes/images are analyzed. Using this rapid and simplified procedure, 47 YACs have been mapped onto chromosome 21 thus far. The mapped probes include 12 known markers (superoxide dismutase, collagen) and structural landmarks (telomeres and centromere). To confirm the order of a dense population of YACs within the Down's syndrome region, a two-color mapping strategy is used that involves locating an anonymous YAC relative to one or two known markers on metaphase chromosomes. This chromosome 21 metaphase map has a 1-2 Mb resolution, and the FL measurement of each probe has a typical standard error of 0.5 Mb. (RPIS 5063(H))

305. Strand-Specific Orientation of Satellite DNA Sequences Determined by Fluorescence In Situ Hybridization

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A modification of the fluorescence in situ hybridization (FISH) is used to demonstrate that satellite DNA sequences have distinct patterns of orientation on specific chromosomes. Some chromosomes, usually those with large blocks of tandem repeats, have sequences aligned in both the 5' to 3' and 3' to 5' directions. Other chromosomes have sequences aligned in the same orientation in a head-to-tail fashion. As the resolution of the FISH method is not absolute, the latter pattern must be considered to be the predominant orientation of the repeat. This method does not detect very low numbers of repeats oriented in the opposite direction. It is known that many of the ubiquitous repeats such as Alu are aligned in both the 5' to 3' and 3' to 5' directions. As expected, the in situ hybridization pattern of these repeats was essentially the same in appearance with the strand-specific method as with the standard protocol for FISH. The alpha satellite, beta satellite, and simple sequence repeats of the classical human satellite DNA sequences demonstrated the chromosome dependent pattern described previously. That is, some of the chromosomes showed hybridization to only one chromatid, while a few of the major heterochromatic sites of other chromosomes, most notably 1, 9, and/or 16, had fluorescent signals on both chromatids. The major satellite DNA of mouse and the nontelomeric locations of the telomeric sequence in some mammalian species also have a strand-specific orientation. (RPIS 5063(I))

306. Genome Organization and Function

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\$416,000

The mechanisms for organizing the mammalian genome and the genetic and nonmutational alterations accompanying abnormal phenotypic change are important aspects in defining the effects of energy-related technologies. Determining the genetic variability in these mechanisms provides a rational basis for establishing thresholds for toxic substances, for making valid cross-species extrapolations, and for eventually identifying individuals at risk.

This project is determining the molecular mechanisms by which higher organisms organize and express their genetic information. Applications of these basic investigations include the development of novel approaches for detecting human genetic diseases and for measuring the effects of low level ionizing radiation and carcinogen exposure. A combination of biochemical, biophysical, and recombinant DNA techniques is being used to identify, isolate, and determine the roles of DNA sequences involved in long range genomic order.

Current efforts focus on determining the organization and function of human repetitive DNA sequences. Major achievements include (1) the demonstration that the human telomere sequence (TTAGGG)_n, identified and isolated by these researchers is the vertebrate telomere and (2) the cloning of 100- to 250-kb human telomere fragments as yeast artificial chromosomes. Future studies will be directed toward defining and isolating other "functional" repetitive DNA regions such as centromeres. (RPIS 4718)

307. Chromosomal Organization of Human Repetitive DNA Sequences

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This project is investigating the chromosomal organization of repetitive sequences, primarily simple repeats (microsatellites) that are generally highly polymorphic within the human genome. Multiple representation human chromosome-specific cosmid libraries have been constructed as an effort of the National Laboratory Gene Library Project. A Biomek robot was used to make approximately one-fold representation high density gridded arrays of the chromosomes 16 and Y cosmid libraries. The grids have been screened by hybridization to all possible mono-, di-, and trinucleotide repeats, as well as to other more complex repeats such as Alu, Ll, THE, and a variety of satellite sequences. A database is being generated that will contain the identity of all clones found to be positive for each repetitive probe. This approach enables comparative studies of the frequency of specific repeats on human chromosomes 16 and Y and provides information concerning the coincident linkage of different repeats on fragments of DNA approximately 40,000 base pairs in length. Identification of microsatellite-containing clones within the Los Alamos National Laboratory chromosome 16-specific cosmid library links potentially highly informative genetic markers onto the emerging physical map. These results should help to integrate the physical and genetic maps, as well as facilitate the rapid localization of disease loci on human chromosome 16. (RPIS 5063(A))

308. Construction and Characterization of Human Genomic Yeast Artificial Chromosome Library with a Low Frequency of Chimeric Clones

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Yeast artificial chromosomes (YACs) have been constructed using DNA isolated from an apparently normal, spontaneously transformed human lymphoblast cell line, GM 130 (46XY). High molecular weight DNA was prepared in low melt agarose plugs, partially digested by competition of EcoRI with EcoRI Methylase, ligated to YAC vectors pJS97 and pJS98, and transformed into *S. cerevisiae* strain YPH 250. Approximately 40,000 YACs with an average size of 180 kb have been identified, which is estimated to be two times the coverage of the genome. The frequency of chimeric YACs was estimated by fluorescence in situ hybridization (FISH) to human metaphase chromosomes. Fifteen of sixteen YACs resulted in a single, discrete FISH signal on homologous chromosomes. The remaining YAC resulted in two FISH signals in ~50 percent of the metaphases. This could be due to a chimeric clone or to the presence of repetitive sequences on the YAC, since the FISH signals were located at the telomeres of the chromosomes. If the YAC is a chimera, then the frequency of chimeric clones may be up to 6 percent in this library. The availability of nonchimeric YAC clones will facilitate construction of accurate physical maps of human chromosomes. (RPIS 5063(J))

309. A Loosely Coupled, Distributed Laboratory Notebook for the cDNA Community

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There are many precedents for the use of commercial database management systems to provide laboratory support for mapping and sequencing, and there are several central repositories for map and sequence data. This project is developing a distributed, loosely coupled database to link collaborating cDNA researchers into a network for localized project support, data sharing across projects, and global resource management. A database schema and a collection of interactive tools have been designed to provide management of cDNA clones, sequencing experiments, sequences, mapping experiments, and features. The database schema consists of a core of objects, relationships, and attributes common to all projects, and a noncore portion customizable by individual labs. The interactive tools are being built around the schema core and are customizable in terms of behavior. This approach was taken in the interest of using the database and interface as a linking node at multiple sites engaged in various activities.

When sequence data are entered, vector sequences, cloning artifacts, and repeats are tagged. Sequence similarity and homology detection are time-consuming operations and the subject of much research. This approach performs comparisons using packaged software (such as BLAST or FASTA) and records results as time-stamped sequence features with annotation for beginning, length, statistical similarity, etc. All values are obtained by parsing BLAST/FASTA output and are subject to user editing and confirmation. Because databases can be generated for any interesting sequences for BLAST/FASTA, one can use a single, uniform mechanism for detecting vector, repeats, cloning artifacts, previously encountered sequences, and Genetic Sequence Data Bank (GenBank) homologies. Further, the results of prior repeat homology comparisons can be used to filter GenBank homologies to eliminate homologies due only to repeats. Time stamping allows users to rerun homology comparisons when BLAST or FASTA databases are regenerated.

With respect to the community of collaborating cDNA researchers, commonality in the core database schema and the interface tools promote data sharing (as well as shared software) between and among projects. Sequence similarity to remote collections is detected by the same mechanism used to insure sequences are locally unique, and this should avoid duplication of sequencing effort. Centralized data management suggests one model for managing distributed, megabase sequencing projects. The current effort is a prototype investigation of a loosely coupled federation of locally controlled databases that promotes cooperation and collaboration. (RPIS 5063(K))

310. Construction of Restriction Maps Using Simulated and Real Data

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GRAM (Genomic Restrict Map Assembly) is a software tool that takes as input fragment data for a set of clones and outputs one or more possible partial restriction maps. The algorithm uses two steps: (1) determine the set of unique fragments and (2) permute the fragments such that the maximum number of fragments within each clone is contiguous. Due to the uncertainty in the data, step 1 cannot always be determined perfectly; the user can query the data through an interactive interface and detect these anomalies. Step 1 uses an algorithm based on clustering techniques, step 2 uses a modification of the shuffle routine used for sequence assembly, and the graphics are a modification of the graphics written for a previous restriction map assembly system.

This project shows results from simulated data and from experimentally derived chromosome 16 data, as follows: (1) through simulated input data, if no uncertainties are in the data, GRAM gets the correct solution; (2) by adding uncertainty to the data, GRAM still arrives at a solution that is close to

optimal, and that it is generally easy to detect the source of uncertainty in the data using the interactive graphics; (3) examples where GRAM was able to detect anomalies in real data, such as repeats and chimeric clones; and (4) some restriction maps assembled from real data. (RPIS 5063(L))

Law Center

311. Ethical, Legal, and Social Issues Projects

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This project assists in coordinating the DOE program on the ethical, legal, and social issues (ELSI) raised by the Human Genome Project. It helps to establish the direction of the DOE ELSI program, serving as a liaison with grant recipients and potential grant applicants, participating in the review of grant preapplications, helping to arrange peer review and technical evaluations of grant proposals, developing additional activities in support of the program, and representing DOE at meetings of the DOE-National Institutes of Health Joint ELSI Working Group and other ELSI conferences and workshops. (RPIS 5527)

Life Sciences Division

312. Automated Methods for Large Scale Physical Mapping

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The Center for Human Genome Studies (CHGS) at Los Alamos National Laboratory (LANL) produces high resolution gridded membranes for screening cosmid and yeast artificial chromosome (YAC) libraries. The demand for these membranes has been steadily increasing and is projected to drastically increase with the construction and distribution of additional libraries. Since March 1992, a prototype automated system developed at LANL has been producing gridded membranes from its chromosome 16 cosmid library. The system produces eight duplicate membranes in 2.5 hours, with each membrane representing up to 16 plates of the cosmid or YAC library. A technician is required only to provide the initial setup. Hardware and software improvements to the prototype, to improve user friendliness, permit random order presentation of microtiter plates and list correctly completed plates at the end of a gridding session. The addition of blunt tipped gridding tools now allows the gridding of YAC libraries. The ability to replicate libraries, another frequently repeated task at the CHGS, has been added. This addition required that another pair of microtiter plate dispenser/restackers, a second barcode reader, and software routines also be added.

Ongoing modifications to three system components on the prototype will increase system throughput. Increasing the size of the membrane holders permits the gridding of twelve membrane copies from each plate presentation and thus reduces

setup and cycling time. An additional tool drying station, along with a third gridding tool, permits increasing robot speed and allows sufficient time for the gridding tools to dry between microtiter well sampling. The project is also exploring the possibility of converting to high density microtiter plates (384 well) with matching gridding tools. This would result in an immediate 4-fold increase in throughput.

Steps are being taken to establish a Cooperative Research and Development Agreement with an industrial partner to provide commercial availability of the project's gridding system.

The second generation is designed to be flexible and modular and allow for the facile implementation of different tasks. The components for this system include a selective compliance assembly robotic arm (Adept Model 604S), a plate stacking system that is easily modified to accept different types of microtiter plates, and an automated subsystem for tool cleaning. An expert system, as the user interface, encourages exploration of rules for automatic control of the biological decisions. Data flow between computer databases is incorporated. (RPIS 5280)

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Biology Division

313. Human Genome Distinguished Postdoctoral Fellowships

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The Human Genome Distinguished Postdoctoral Fellowships were initiated in FY 1991 by DOE-OHER to support research by recent doctoral degree recipients on projects related to the DOE Human Genome Project. Fellowships of up to 2 years are tenable at laboratories having research programs supportive of the Human Genome Project. Fellows earn stipends of \$37,500 for the first year and \$40,500 for the second. Eligible applicants must be U.S. citizens or permanent resident aliens and must plan to receive their doctoral degrees within 3 years of starting their fellowships. Principal investigators at host laboratories must be supported by OHER in the amount of at least \$150,000 per year.

Oak Ridge Institute for Science and Education (ORISE), administrator of the fellowships, prepares and distributes program literature to universities and laboratories across the country, accepts applications, convenes a panel to make recommendations for awards, and issues stipend checks to fellows. During the first program cycle in FY 1991, 42 applications were received. The review panel identified 10 finalists from which DOE chose 5 award winners. The new fellows received their doctoral degrees in biophysical chemistry, molecular biology, computer science, and bioengineering and are serving their fellowships at four different host laboratories. The deadline for each fiscal year fellowship cycle is February 1.

For more information or an application packet, contact Linda Holmes at the Science/Engineering Education Division, ORISE, Rm. 45, P.O. Box 117, Oak Ridge, Tennessee 37831-0117, (615) 576-4805. (RPIS 5393)

Oak Ridge National Laboratory

Oak Ridge, TN 37831

314. Detection of Luminescence from Lanthanide Ions as Labels for DNA Sequencing

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This research project's goal is to develop a sensitive and readily automated method of detecting labeled DNA fragments that can be applied to sequencing. A new luminescent labeling system is being developed that can be used with capillary electrophoresis.

The lanthanide ions [Ln (III)] used for labeling include Eu(III), Tb(III), Sm(III), and Dy(III). These ions are being attached to DNA with a derivative of the macrocyclic chelating agent 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA). Naphthalene, attached to DOTA, functions as an antenna to relay excitation energy to the excited states of the Ln(III) ions. The luminescent states of these ions are f-f in origin, and the narrow emission line widths allow multiple labels to be detected simultaneously with minimal interference. Furthermore, the Ln(III) excited states have long lifetimes that allow the use of gated detection for high background discrimination.

Energy transfer from naphthalene to the Ln(III) ions has been demonstrated in a naphthyl derivative of complexes of Eu(III), Tb(III), Sm(III), and Dy(III) with the chelating ligand diethylenetriaminepenta-acetic acid. Oligonucleotides labeled with Ln(III)DOTA complexes are tested as primers for DNA polymerase in the Sanger sequencing procedure and in polymerase chain reaction amplification. Detection limits for labeled oligonucleotides are determined with capillary gel electrophoresis on-column detection. (RPIS 5513)

315. Using Scanning Tunneling Microscopy to Sequence the Human Genome

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\$480,000

This project involves the operation and continued development of scanning tunneling microscopies (STMs) for basic physics

research related to health and environmental problems. Methodologies to facilitate atomic and molecular studies important in sequencing the human genome and to provide other technology applications in surface science are being developed. An STM with single-atom resolution is used to image atomic structure on surfaces, to alter atomic positions, and to probe the dynamic phenomena caused by collective electron motion and motion of ions. Objectives include extending STM capabilities to a wider range of materials, identifying atomic species, and studying biological samples. (RPIS 4985)

Biology Division

316. DNA Sequence Analysis by Solid-Phase Hybridization

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\$405,000

This project develops the use of arrays of oligonucleotide sequences on solid supports for use in DNA sequence analysis. Complete sets of all possible sequences of a given length or any combination of selected sequences are prepared, with each sequence being identified by its position in the array. While covalently attached to the support, the probes are hybridized with target DNA under conditions designed to optimize mismatch-free duplex formation. The target DNA fragments carry labels detectable by optical or mass spectral characteristics. Arrays containing complete sets of sequences eight or more nucleotides in length are used to implement DNA sequencing by hybridization. Smaller arrays of selected sequences can be used for mapping, fingerprinting, and other DNA diagnostic applications. Techniques are being developed for the synthesis of microscale arrays containing complete sets of sequences in a few square centimeters. (RPIS 5346)

317. DNA Sequencing Using Stable Isotopes

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\$535,000

**Chemistry Division*

This project involves developing a new DNA sequencing approach to determine the sequence of 1×10^7 to 6×10^8 nucleotides per day. In this procedure, stable isotopes of iron, tin, and several lanthanides are used to label either DNA or the oligonucleotide probes that locate DNA fragments after electrophoresis. The use of stable isotopes eliminates the

problems associated with radioisotopes, including radiation exposure to personnel, the costs of radioactive waste disposal, and the need to cope with short half-lives of reagents that contain radioisotopes.

Resonance ionization spectroscopy (RIS) is used to localize and quantify these elements and all their isotopes. The sensitivity and selectivity of RIS is comparable to that of the radioisotope and fluorescent methods currently used. Furthermore, the multiplex method of DNA sequencing is adapted for use with stable isotopes so that 20–40 labels can be used simultaneously. This requires that the maximum number of stable isotopes of a given element be attached to a series of oligonucleotides in a stable configuration so that the label does not interfere with accurate hybridization.

One section of this study involves the development of chemical methods to incorporate iron, tin, and the lanthanides into organometallic compounds that can be attached to DNA. A second section consists of an evaluation of two analytical methods used to detect and quantify stable isotopes: sputter-initiated resonance ionization spectroscopy measures fractions of a monolayer, and laser atomization resonance ionization spectroscopy measures several monolayers of the sample surface. Other properties of these two methods are also important and are being considered in the evaluation process.

A third aspect of this study is the modification of the gel electrophoresis procedure to optimize the amount of DNA that appears at the gel surface after the electrophoretic separation of the DNAs and the subsequent drying of the gel. Ultra-thin horizontal gels and capillary gel columns may be evaluated for their ability to accomplish electrophoretic DNA separation and detection. A fourth component of this project is the development of data management methods that enables the large volumes of nucleotide data obtained by RIS to be assembled into sequence information. This project requires the collaboration of physicists, chemists, molecular biologists, and computer scientists. (RPIS 5155)

318. Mapping in Mouse-Human Homologous Regions

E.M. Rinchik

R.P. Woychik

L.J. Stubbs

L.B. Russell

M.L. Mucenski

E.C. Uberbacher

R.J. Mural

(615) 574-0953

\$600,000

Comparisons of murine and genetic maps have revealed that a number of linkage groups has been conserved throughout evolution. The mouse can be especially useful as a model for physical and functional analyses of the human genome. This project is designed to define further these genomic homologies and to begin construction of directly comparable, fine structure physical and functional maps. Physical mapping efforts are focused initially on mouse chromosome 7, with special emphasis on regions with well-established human homology. Physical maps are centered on conserved human cDNA clones

in order to allow direct comparisons between mouse and related human regions and to facilitate their eventual correlation with the phenotype maps of both species. To augment the capability for functional translation of physical maps, the project explores the feasibility of developing efficient and cost-effective methods for expanding the mouse-mutation resource, genome-wide, by generating targeted mutations, as well as germline deletion complexes, in embryonic stem cells. Computerized databases, as well as new methods in artificially intelligent DNA sequence analysis, are used to store, interpret, and advertise all data and resources emanating from this project. (RPIS 5657)

319. Generating a Comparative Physical Map of Mouse Chromosome 7

L.J. Stubbs

E. Rinchik

E. Generoso

(615) 574-0848

\$100,000

Detailed comparisons of murine and human genetic maps have revealed that a number of linkage groups has been conserved, despite extensive chromosome reorganizations that have occurred throughout evolution. Whatever their evolutionary significance, the similarities and differences existing between murine and human genomes may provide valuable information regarding the structure and function of both. This project expands the basis of those comparisons and begins the translation of that genetic basis into a detailed series of directly comparable physical maps.

Efforts are focused on the analysis of mouse chromosome 7 (Mmu 7), with special emphasis on regions with well-established human homology. The maps are centered on conserved, mapped human cDNA clones to maximize potential for direct interspecies comparisons and to facilitate correlations with phenotype-based genetic maps of both species. The specific goal of this task is the complete physical linkage of markers, first throughout the well-marked segments of homology with HSA 19q13, 11p15.4-15.5, and 15q, and eventually throughout the length of Mmu 7.

This task is part of a multi-investigator program that combines genetic and physical mapping of mouse chromosomes with new strategies of germline mutagenesis. The program has two major goals: (1) to contribute to the genetic and physical mapping of human chromosomes by physically mapping the mouse genome within mouse-human homology regions and (2) to complement other mouse genetics centers by developing a system for relatively low cost, major escalation of the mouse-mutation resource (targeted mutations and chromosomal rearrangements) that can be used by any present or future member of the mammalian-genome analysis community. (RPIS 5622)

Engineering Physics and Mathematics Division

320. GRAIL: An Intelligent System for DNA Sequence Analysis

E.C. Uberbacher

(615) 574-6134

\$262,000

This project is developing artificial intelligence-based methods for the recognition of biologically significant features in genomic DNA sequence data. The project is also constructing an integrated analysis system based on these methods for the automated assembly of hypothetical genes and tentative interpretation of their function. The focus is on two central areas of DNA sequence analysis: (1) the use of machine learning techniques to improve the basic pattern recognition technology for the identification of sequence regions that correspond to genes and other biologically important features and (2) development and implementation of an expert system to facilitate application of recognition tools and the intelligent automated assembly of recognized genetic features into hypothetical models for gene structure and function. Such a system will be a significant improvement over current computer-assisted systems that rely on standard deterministic programming methods and will be better able to deal with the complexities and inconsistencies inherent in real sequence data. The improved feature recognition tools developed through this effort are valuable for ongoing experimental gene localization activities as well as software development. The integrated system will be implemented on massively parallel platforms at Oak Ridge National Laboratory and will be accessible through Internet to the genome community. Software will also be distributed to other genome centers and individual laboratories. (RPIS 5660)

Health and Safety Research Division

321. Vacuum Ultraviolet Ionizer Mass Spectrometer for Genome Sequencing

C.H. Chen

M.G. Payne

K.B. Jacobson

(615) 574-5895

\$256,000

This project is designed to construct a new high resolution mass spectrometer equipped with a vacuum ultraviolet (VUV) photonionizer for use in human genome sequencing. Potential advantages of this method include eliminating the need for gel electrophoresis and radioactive labels and speeding up the DNA sequencing rate. This method conceivably could be used to sequence DNA segments up to 3,000 nucleotides long.

Major steps for DNA sequencing by this approach include (1) incorporating organometallic compounds such as ferrocene into DNA molecules by means of the primer sequence, using the standard dideoxy terminator method; (2) developing methods to deliver ferrocene-tagged DNA segments to a mass spectrometer ionization zone without any DNA-segment decomposition; (3) using a VUV or UV coherent beam to ionize DNA segments

without producing any fragmented ions; and (4) sending the ions produced into a mass spectrometer that can measure molecular weights higher than 100,000 Da.

During the first 3 years of this program, most of the effort will be concentrated on resolving several critically important questions. If results are favorable, a complete facility will be built to do routine DNA sequencing. (RPIS 5512)

322. Human Genome Management Information System

B.K. Mansfield

A.E. Adamson

D.K. Casey

K.A. Davidson

S.A. Martin

D.B. Stinnett

J.S. Wassom

J.M. Wyrick

L.N. Yust

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\$650,000

The Human Genome Management Information System (HGMIS), sponsored by DOE at Oak Ridge National Laboratory, is charged with (1) helping to communicate genome-related issues and research to contractors, grantees, and the public and (2) providing a forum for information exchange among investigators in the Human Genome Project. To fulfill these communication goals, HGMIS produces contractor-grantee workshop reports, DOE Human Genome Program reports, a bimonthly newsletter (cosponsored by the National Institutes of Health National Center for Human Genome Research), and a traveling exhibit of the DOE genome program. HGMIS also supplies support on demand to project administrators in preparing meeting minutes, conducting information searches, writing, and editing. To facilitate progress in the international Human Genome Project, HGMIS disseminates information to individual requestors and refers them to other sources. A textual database of genome-related material is under development.

Workshop reports feature (1) an overview of research presented at the meeting and (2) detailed abstracts of ongoing research. Program reports give background material on the project and on genomics and describe progress in DOE-supported human genome research and development. The newsletter *Human Genome News* features technical and general interest articles, meeting reports, project news, genome events and training calendars, and grant and fellowship announcements. Working with the international Human Genome Organization and Genome Database, HGMIS also reports international genome project news and major mapping database information in the newsletter.

HGMIS invites comments and suggestions from the research community and the public about its documents and services, which are available upon request and without charge. (RPIS 5166)

Instrumentation and Controls Division

323. Genomic Instrumentation Development: Detection Systems for Film and High Speed Gel-Less Methods

J.B. Davidson

R.S. Foote

(615) 574-5599

\$170,000

Researchers are seeking ways to make conventional gel and film viewing easier and more efficient because these techniques will probably be used in mapping and sequencing for many years, especially in smaller laboratories. New approaches to high speed gel-less sequencing are also being explored.

Two simple but effective devices have been invented to aid in reading film—the Un-smiler and the Un-dimmer. The Un-smiler is an anamorphic optical viewer that straightens the tilt “smiling” in sequencing gels and provides a horizontal reticle to aid in reading crowded gels. The Un-smiler can also be used for vertical magnification to give improved band separation. The Un-dimmer is an inexpensive contrast-enhancing viewer used to detect bands or spots that are almost invisible on a clear film background, nearly doubling contrast. In addition to sequencing and blotting applications, the device could be used in radiology (e.g., for bone imaging) and industrial radiography. The principles used in both hand-held viewers can be applied to improve electronic densitometry of film.

A new, simplified fast scanner for sequencing films is being tested; it will provide sequence directly, without storage and manipulation of the image in computer. One DNA sample is expected to yield raw sequence about 1 m after scanning starts. The scanner is expected to be inexpensive compared with software-intensive image analysis systems. Given “good” gels, multiplexing can be used to sequence several samples simultaneously.

To develop new approaches to high speed gel-less sequencing, researchers are collaborating on a project with Oak Ridge National Laboratory (ORNL), Biology Division, to use a lens-less radiation microscope (developed under OHER sponsorship) to contribute to the special detector design needed to implement microscale sequencing by hybridization.

Researchers are continuing to develop a high speed sequencing approach (initiated under ORNL Director's Fund sponsorship) involving high speed vacuum electrophoresis and detection of biochemically produced fragments. In principle, the sequence of a 200- to 300-bp sample could be obtained in less than 1 s without gel or film. If successful, the new separation and detection method could be combined with a biochemical robot for continuous or quasi-continuous sequencing at an estimated rate of more than 10^6 bp/day. The ORNL biology group is providing expertise and will supply specially labeled DNA samples. Assistance in mass spectro-metry has been provided by members of the Mass Spectrometry Section of the ORNL Analytical Chemistry Division. (RPIS 4277)

Pacific Northwest Laboratory Richland, WA 99352

Chemical Sciences Department

324. Ion Cyclotron Resonance Mass Spectroscopy of DNA Molecular Ions

R.D. Smith

C.G. Edmonds

J.A. Loo

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\$154,000

This project is developing new approaches to DNA sequencing and analysis. New developments in combined ion cyclotron resonance (ICR) mass spectrometry and electrospray ionization (ESI) provide the basis for the formation, isolation, and extended trapping of single highly charged DNA molecular ions with molecular weights well into the megadalton range. This approach, termed single-molecule analysis by mass spectrometry (SMAMS), will use new ESI-ICR instrumentation developed at Pacific Northwest Laboratory.

The SMAMS concept involves trapping a single multiply-charged, single-stranded DNA anion in an ICR cell, where its mass-to-charge ratio (m/z) is measured with high accuracy. The m/z is then followed as the isolated molecular ion is subjected to an extended series of rapid reactive degradation steps (i.e., single oligonucleotide bases are removed in stepwise fashion). This approach circumvents limitations due to isotopic and other contributions and provides a basis for rapid DNA sequence determination, extending to segments as long as 25,000 bases.

The project is investigating ion-molecule reactions and other processes that can accomplish a stepwise reactive degradation of gas phase DNA anions. Successful development could greatly reduce the cost and enhance the speed of DNA sequencing, potentially allowing for sequencing kilobase-size DNA segments in a few minutes. In addition, such methods would provide site-specific information on DNA chemical modifications to individual molecules, information not obtainable by any existing methodology. (RPIS 5658)

Life Sciences Center

325. GnomeView: A Graphical Interface to the Human Genome

R.J. Douhart

J.E. Pelkey

D.A. Thurman

(509) 375-2653

\$240,000

GnomeView is a graphical user interface that displays color representations of genomic maps for review, analysis, and manipulation. GnomeView's local network-model database contains chromosome maps as well as high level descriptive information taken from both GenBank and the Genome Data Base (GDB). GnomeView locates and presents maps and other queried information in an organized and easily used format. Displays are available

for one chromosome or any combination of chromosomes, including the entire human karyotype. GnomeView displays GenBank tables as color-coded objects mapped to a sequence representation. All maps are displayed in windows with full zoom and pan control.

GnomeView architecture is designed to represent many different types of genomic maps. An internal database management system stores map objects and information about their linkages; however, GnomeView is primarily an interface and not a database repository. In the future, remote on-line access to GenBank, GDB, and other genome databases as primary map information sources may be established. (RPIS 4987)

Biotechnology: Human Genome

Offsite Grants

Adelaide Children's Hospital North Adelaide, South Australia 5006

Department of Cytogenetics and Molecular Genetics

326. Correlation of Physical and Genetic Maps of Human Chromosome 16

G.R. Sutherland

(618) 267-7333

International: 61/8-204-7333

\$200,000

Forty-nine mouse/human hybrids containing various portions of human chromosome 16 have been constructed. The majority of the human cell lines used as parents in these fusions contained balanced translocations identified by cytogenetics service laboratories. The breakpoints in these hybrids, together with the four major fragile sites on this chromosome, have been ordered by mapping genes and anonymous DNA probes. Mapping efforts now concentrate on a polymerase chain reaction approach, utilizing multiplexed sets of sequence-tagged site (STS) markers and CA-repeat microsatellite sequences. At this stage, chromosome 16 has been divided into 42 regions by mapping approximately 200 markers, including cosmid contigs developed at the Los Alamos National Laboratory. The physical mapping of a large series of probes typed in the CEPH pedigrees has allowed the construction of a detailed genetic map of the complete chromosome. The detail of this map is being extended by using highly informative CA-repeat microsatellite sequences. Several sequences have been isolated, and two have been typed on the CEPH panel. This extensive hybrid cell panel, together with the detailed physical mapping now possible, is being used to study (1) cloning of constitutional chromosome breakpoints, two of which are presently amenable to analysis and one of which is associated with a genetic syndrome; (2) cloning of cancer-associated breakpoints on human chromosome 16 (a number of collaborative projects are in progress); (3) cloning of Batten disease, in a region where

detailed physical and genetic mapping is in progress; (4) cloning of fragile sites (The rare folate-sensitive fragile site, FRA16A, has now been localized to a 400kb *SalI* fragment. Cloning of this region is in progress); and (5) the construction of cosmid contig maps spanning chromosome bands. (Extensive probeings of high density dot blots of cosmid clones with probes mapped in bands 16q22.1 and 16p12 are in progress.) (RPIS 10087)

Advanced Technology Applications, Inc.
Research Triangle Park, NC 27709

327. Interactive DNA Sequence Processing for a Microcomputer

W. Denloff

(919) 248-1818

\$49,610

DNA and biosequences are being determined faster than they can be compared and analyzed. Present techniques for rigorously searching a large database are costly and time consuming. Under all plausible growth projections, the problem will soon become overwhelming. A custom, very large scale integrated circuit that could be used for high speed comparison, analysis, and interpretation of DNA and protein sequences has been designed. The systolic array can, in a single pass, scrutinize each segment of every biosequence in a database to determine its homology to any segment of an input pattern according to a statistically rigorous criterion. Phase I research includes designing and prototyping a low cost biological sequence comparative analysis node (BioSCAN) printed circuit board for an IBM-compatible AT personal computer. In addition, software enabling the board to interface with commonly used, public domain software packages (e.g., FASTA or BLAST) is being developed. Finally, the performance of the system in actual laboratory settings is being evaluated against current techniques.

The proposed BioSCAN system will scan a database at a sustained rate of 2.5 million sequence elements per second, or approximately 1,000 times faster than the best software available. The result of a BioSCAN search may be useful by itself or may serve as prefiltered input for further analysis. A cost/performance ratio 10,000 times lower than that of a massively parallel or vector supercomputer is expected. The performance increase afforded by this BioSCAN system will increase the productivity of molecular biologists, and the interactive capability will change their fundamental approach to the sequence analysis problem. (SBIR)

Affymax Research Institute
Palo Alto, CA 94304

328. Spatially Defined Oligonucleotide Arrays

S.P.A. Fodor

(415) 496-2300

\$50,000

This Phase I research project involves the construction of spatially defined arrays of oligonucleotide probes and the use of

these arrays to study DNA sequencing by hybridization. Newly developed techniques in light-directed polymer synthesis are being applied to the construction of oligonucleotide arrays, to the exploration of kinetic and solvent-related parameters of target hybridization to the arrays, and to the reading of the positions of hybridization by epifluorescence microscopy. Specific combinatorial synthesis strategies are being designed to address experimental issues of parallel hybridization. Completion of this work will lead to sequencing instrumentation that could provide order-of-magnitude improvements in DNA sequencing productivity.

Successful completion of this project will lead to a method for rapid and inexpensive fabrication of oligonucleotide arrays. The oligonucleotide arrays can be applied to the Human Genome effort for high throughput sequencing by hybridization, and to other efforts in genetic fingerprinting and genetic mapping. Scale-up of this technology could be used to provide oligonucleotide templates to national, university, and commercial laboratories investigating applications of hybridization technology. The oligonucleotide arrays would find commercial applications in genetic diagnostics. (SBIR)

University of Alberta

Edmonton, Alberta, Canada, T6G 2G2

Department of Chemistry

329. Multicolumn Gel Electrophoresis and Laser-Induced Fluorescence Detection for DNA Sequencing at 64,000 Bases/Hour

N.J. Dovichi

(403) 492-3254

\$125,000

The goal of this research project is to develop a laser-induced fluorescence detector for multiple capillaries in gel electrophoresis separation of DNA sequencing samples. Capillary gel electrophoresis offers the advantage of higher speed and higher resolution separations of DNA fragments than can be achieved with low electric field slab gel technology. Currently, researchers can sequence at 2,000 bases/hour using a single capillary system. By operating 32 capillaries simultaneously, however, sequencing rates of 64,000 bases may be produced with a single instrument. Because this instrument requires only one modest power laser, an electrophoresis power supply, and a computer for data collection, its cost should be quite modest. The small capillary diameter permits only a minute amount of fragment to be loaded onto the capillary without degradation of the separation. Estimates indicated that only 1 to 10 attomole (1 attomole = 1 amol = 10^{-18} mol) of each DNA sequencing fragment can be loaded before column overload effects become significant. To measure fluorescence intensity accurately, the signal-to-noise ratio must be as high as possible; detection limits well below an attomole are required in capillary gel electrophoresis. Three different sequencing systems are applied to DNA samples in capillary gel electrophoresis: (1) a single-laser and single-emission spectral channel system for Richardson and Tabor's sequencing technique, (2) a single-laser excitation and dual-emission spectral channel detector for DuPont's

sequencing technique, and (3) a dual-laser excitation and four-emission spectral channel detector for Smith and Hood's sequencing technique. The sequencing rate routinely exceeds 1,000 bases/capillary and has, upon occasion, been pushed to 2,000 bases. The best detection limits (1,400 molecules) are obtained using the Richardson/Tabor sequencing technique with a 750- μ w helium-neon laser ($\lambda = 544\text{nm}$) and a cooled PMT.

A five-capillary, laser-induced fluorescence detector based on a sheath flow cuvette is being designed. In this system, a single laser excites fluorescence from the capillaries, a single optic collects fluorescence, a single spectral filter rejects scatter light, and five high sensitivity photodetectors measure fluorescence. A 32-capillary system will be constructed for high throughput sequencing based on the experience with the 5-capillary system. (RPIS 10433)

American Type Culture Collection Rockville, MD 20852

330. Multiplex Mapping of Human cDNAs

W.C. Nierman
D.R. Maglott
(301) 231-5559

\$220,000

To contribute to the "rapid assignment of cDNAs to chromosomes and subchromosomal regions" (DOE Special Research Grant Program Notice 91-7), we are attempting to determine the utility of multiplexing polymerase chain reactions (PCR) for mapping cDNA sequences. Researchers from National Institute of Neurological Diseases and Stroke (NINDS), now at the Institute for Genomic Research (TIGR) have already begun to identify genes expressed in the human brain by partially sequencing cDNA clones from brain libraries. Working in collaboration with the NINDS group, project researchers are using NINDS sequence data to develop methods for rapid localization of newly identified cDNAs to human chromosomes. Researchers are using an ABI automated sequencer to analyze multiplexed PCR products to map four or more sequences simultaneously. Project researchers plan to (1) design PCR primers from the NINDS laboratory-generated sequence data, (2) test the primers for multiplexed specific amplification from human genomic DNA, (3) combine useful primer pairs for multiplexed PCR amplification from a somatic cell hybrid cell mapping panel, (4) determine the presence or absence of the specific amplification products from each cell line DNA by electrophoretic analysis using the ABI sequencer, and (5) analyze the pattern of amplification results from the hybrid panel to identify the chromosomal origin of the cDNA sequence. Multiplexing the amplification reactions and analyzing the reaction products on an ABI 373A automated sequencer generates high throughput with a minimum allocation of resources. In addition to technology development, this project will determine chromosomal assignments for expressed sequence tags (ESTs), provide primer sequence data for subsequent subchromosomal localizations, and generate a broad data set from which to evaluate strategies to identify functional primer sequences from cDNA sequence data. (RPIS 10556)

University of Arizona Tucson, AZ 85721

Department of Chemistry

331. Single-Molecule Detection Using Charge Coupled Device Array Technology

M.B. Denton
R. Keller
M.E. Baker
C.W. Earle
D.A. Radspinner
(602) 621-8246

\$134,000

Successful single-molecule detection relies on a satisfactory signal-to-noise ratio to allow the specific determination of individual fluorescently tagged bases in a flowing stream. Current detection is limited by strong background emission, most notably Raman. Although the fluorescence signal of individual molecules is much stronger than the Raman background, the sheer number of solvent molecules produces noise that inhibits single-molecule detection. Indeed, the process is much like searching for a needle in a haystack.

Effective use of a charge coupled device (CCD) promises significant enhancement of the signal-to-noise ratio. A special CCD mode of operation offers a unique means of detecting relatively bright sources in a large background field. This technique, known as time delay integration imaging, was first used in aerial surveillance by military satellites. In this process, the pixels in the CCD array are clocked or shifted synchronously with the flow of the analyte, much like a high speed photographic technique in which the film is moved across the shutter in the same direction as the object being observed. In this system, the synchronization effect collects the emission from a single species into a single, moving charge packet. The fluorescent signal is enhanced over the background because it is condensed into a sector as small as a one- or two-pixel array, while the background emission is distributed over the entire photoactive surface of the CCD array. Thus, the entire fluorescent signal can be integrated into a charge packet containing background noise only from the immediate vicinity of the fluorescent species. With this technique, the signal-to-noise ratio can be improved by about two hundred- to several thousandfold. (RPIS 10255)

Arizona State University

Tempe, AZ 85287

Department of Chemistry

332. Time-of-Flight Mass Spectrometry of DNA for Rapid Sequence Determination

P. Williams

N. Woodbury

(602) 965-4107

\$269,000

A time-of-flight mass spectrometry technique is being developed for rapid and accurate analysis of DNA sequencing mixtures. Intact DNA molecules are volatilized by pulsed laser ablation of frozen aqueous DNA solutions at 532, 578, or 589 nm. The ablated DNA molecules are ionized by attachment of sodium ions. These are produced by the ablating laser pulse by resonant multiphoton ionization of sodium atoms from the vaporized solution. Intact DNA up to molecular weight ~ 6 MDa (~ 9 kbp) has been volatilized, and DNA molecular ions up to 18,500 Da (28 bp) have been detected using this combination of techniques. The upper mass limit of the mass spectrometer is being extended to at least 300 kDa, initially by increasing the ion impact energy on the electron multiplier detector. Because secondary electron production by ions more massive than ~ 30 kDa is inefficient or nonexistent, the project is exploring new detector technology for massive ions using conversion dynode surface coatings that efficiently emit secondary ions. A capability is being developed for high speed DNA sequencing using time-of-flight mass spectrometric ordering of dideoxynucleotide-terminated DNA mixtures produced by the Sanger process. Accurate (3 Da) mass difference measurement techniques are being designed to facilitate error detection in sequence ordering. Simplifications in the biochemical production of sequencing mixtures, made possible by such mass accuracy, are being explored. (RPIS 10430)

Atom Sciences, Inc.

Oak Ridge, TN 37830

333. Increased Speed in DNA Sequencing by Utilizing Laser Atomization Resonance Ionization Spectroscopy and Sputter-Initiated Resonance Ionization Spectroscopy to Localize Multiple Stable Isotope Labeled Fragments

H.F. Arlinghaus

(615) 483-1113

\$494,436 (2-year funding)

Major improvements to today's slow, labor-intensive DNA sequence determination procedures are critically needed as there are approximately 3×10^9 nucleotide pairs in the human genome. Given a fast, sensitive, and selective detection method, large numbers of stable isotopes could be used to label DNA, thereby multiplexing the separation process and providing a new, much faster procedure for localizing DNA after electrophoresis. At the Oak Ridge National Laboratory, methods have been developed for synthesizing iron and tin labels for oligo-

nucleotides, with other element labels being developed. In Phase I, laser atomization resonance ionization spectroscopy (LARIS) and sputter-initiated resonance ionization spectroscopy (SIRIS), which utilize lasers tuned to specific energy levels of the selected element, are being used to demonstrate detection of subattomole quantities of iron and tin labeled DNA with excellent lateral and mass resolution. Both LARIS and SIRIS can potentially make a strong contribution both to DNA sequencing and to any other procedures that require detection and localization of DNA or of an oligonucleotide that hybridizes to DNA. Because the ion beam and the laser beam used in the two atomization processes can be focused to 2 to 3 microns, the electrophoresis gel length needed for sequencing can be reduced from the 50 to 100 cm length currently used to 5 cm or smaller. This reduction leads to shorter electrophoresis times, the use of smaller quantities of DNA, less background, and faster analysis. Using higher repetition rate lasers (to 1 kHz using excimers, to 10 kHz using Cu vapor) it should eventually be possible to detect more than 10^7 bases per 24 hours.

Utilizing resonance ionization spectroscopy (RIS) to localize multiple stable isotope-labeled fragments significantly increases the rate of sequencing and makes the goal of mapping the entire human genome achievable. Advances in sequencing technology will have a major impact on the cost and effectiveness of both research and practical applications in a very wide range of genetic topics. Technique users will be at national, university, and private laboratories. A highly significant business could develop in supplying instrumentation and services for localizing multiple stable isotope-labeled fragments to research and clinical laboratories. (SBIR)

Baylor College of Medicine

Houston, TX 77030

334. National Study Conference on Genetics, Religion, and Ethics

J.R. Nelson

C.T. Caskey

H. Bouma III (Institute of Religion)

(713) 797-0600

\$70,000

The main objective of this project is to elucidate four of the main issues raised by the Human Genome Project (HGP) and related genetic research and applied technology. These issues are as follows: (1) How does emerging genome information challenge traditional religious concepts of human nature, behavior and moral responsibility, even as religious insights contribute to the researcher's understanding of the value and inviolability of human life? How are the current practices of positive eugenics, as well as ideology of eugenics, to be regarded? (2) What measures can ensure respect for personal privacy and patient autonomy in the performance of genetic screening, testing, and counseling? What constraints should be placed on the professional practice of confidence and

discretion in disclosing genetic information to persons who have been tested and to their families? (3) What effects may HGP add to the problem of reproductive choices that are inevitable, given preconceptual testing and prenatal diagnosis? What aids to moral understanding and guidance are forthcoming and agreeable? (4) What guidelines can be developed for practicing physicians when they apply genome knowledge in new ways to diagnosis and therapy and must thus educate their patients and the public in the meaning, problems and promises of molecular genetics? The distinctive character of this project is its inclusion of theologians, ethicists, and representative leaders of religious bodies along with researchers in molecular genetics, clinical physicians, and framers and students of social policy. The project is expected to enable people of diverse disciplines, professions, viewpoints, and religious beliefs to discover common, practical ways of understanding certain implications of HGP. The project's hypothesis is that the traditional and evolving theology and ethics of religious communities are relevant to the findings and medical applications of genetic science, while the emerging data of the human genome may in turn indicate modifications of traditional beliefs about human life and behavior. Cultural and environmental influences are also considered in analyzing the causes of aberrant behavior and disease. (RPIS 10480)

Department of Cell Biology

335. Genome Assembly Manager

C. Lawrence

(713) 798-6226

\$483,000

The long-term goal of this research is to develop an integrated software environment to support the activities of laboratories engaged in large scale DNA sequencing. This project addresses the problem of sequence reconstruction when using a "random" sequencing strategy. An interactive X Window-based application called the Genome Assembly Manager (GAM) is being developed in collaboration with a sequencing core laboratory in the Baylor Human Genome Center to support the assembly of sequences in large scale sequencing projects. Underlying GAM is a Fragment Assembly Engine based on a rigorous theoretical foundation developed at the University of Arizona. The goal of GAM is to allow the technicians, molecular biologists, and project managers to interact efficiently with the data and sequencing strategies involved in large scale sequencing. GAM is one component of the integrated software environment these researchers are developing to support the Human Genome Project. (RPIS 10438)

Institute for Molecular Genetics, Texas Medical Center

336. Mapping and Ordered Cloning of the Human X Chromosome

C.T. Caskey

(713) 798-4774

\$525,000

The overall goal of this project is to isolate the human X-chromosome in overlapping segments of cloned DNA. This process involves the production of large insert clones using the yeast artificial chromosome (YAC) vector system, regional assignment of YACs to specific portions of the chromosome, and the characterization of contiguous arrays of clones. YAC library construction is performed using DNA from both human-hamster somatic cell hybrids, retaining the entire X-chromosome (or portions of it) as their only human material, and from flow-sorted human X chromosomes. Additional YAC clones are collected from other pre-existing libraries, such as the total human genome library constructed at Washington University in St. Louis and recently transferred to Baylor University. Fragments of YAC DNA are specifically amplified from total yeast DNA using *Alu*-polymerase chain reaction (*Alu*-PCR), allowing amplification of sequences located between two adjacent *Alu*-repeats. Such *Alu*-PCR probes allow regional assignment of each clone via the hybridization to somatic cell hybrid mapping panels dividing the X chromosome into approximately 40 to 50 subregions (each of ~3 Mbp). Initial attempts to identify long stretches of adjacent clones are performed among clones previously assigned to the same chromosomal subregion and will later be expanded to the entire chromosome. End-probes from each clone are obtained by *Alu*-vector PCR and used for the identification of overlaps. Confirmation and extent of overlaps and quality controls of the used clones are achieved by a variety of methods, including *Alu* and LINE hybridization to digested yeast DNA and by *Alu*-PCR fingerprinting. New methods are planned that will directly identify clones from specific regions of the chromosome, easily produce sequence-tagged sites (STSs) from each clone, and isolate polymorphic genetic markers amenable to assay by PCR in order to place these physically mapped regions onto the genetic map. (RPIS 9862)

337. Isolation of cDNAs from the Human X Chromosome and Derivation of Related Sequence-Tagged Sites

D.L. Nelson

(713) 798-6552

\$198,000

This project is isolating expressed sequences from the human X-chromosome, converting them to sequence-tagged sites (STSs) and associating them with large insert yeast artificial chromosome (YAC) clones. These goals are accomplished through several strategies, and the collection of these data provides STSs for integration into the large scale physical map of the chromosome currently under construction. The collection of cDNAs and their sequences from the X-chromosome constitutes an important goal of genome analysis and provides a rich source of information. The methods proposed to isolate

and characterize genes from this region are general in nature and are applicable to other regions of the human genome. The methods proposed are the following: (1) sublocalization of cDNA-based STSs with X-chromosome localization and identification of associated YAC clones; (2) isolation of human-specific cDNA clones of heterogeneous nuclear ribonucleic acid through the use of somatic cell hybrids retaining the X-chromosome as their only human material; and (3) identification and isolation of expressed regions from YAC clones by hybrid selection of cDNAs and introduction of YAC DNA sequences into cultured mouse L cells, followed by analyzing the resulting RNA for the presence of human-specific expression or through exon-trapping methods.

Sequences are characterized by regional assignment, cross-species hybridization to identify conservation, and DNA sequence-homology analysis. This catalog of genes from the X-chromosome provides significant insight into the organization of the genome, evolutionary relationships of X-chromosomes among mammalian species, and the etiology of many of the hundreds of X-linked human genetic diseases. (RPIS 10649)

**Beckman Research Institute, City of Hope
Duarte, CA 91010**

**338. Improvement and Automation of Ligation-Mediated
Genomic Sequencing**

A.D. Riggs

G.P. Pfeifer

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\$189,000

Ligation-mediated genomic sequencing (LMGS) is a newly developed technique that allows high quality sequence information to be obtained from mammalian cells without cloning. The first step in this technique is to prepare DNA with 5' phosphorylated ends. Maxam-Gilbert cleavage provides such ends and generates sequence information that can be amplified by LMGS. Next, a gene-specific oligonucleotide (primer 1) is used for a primer extension reaction, generating molecules that have a blunt end on one side. Linkers are ligated to the blunt ends, and then the linker-ligated molecules are amplified by an exponential polymerase chain reaction using the longer oligonucleotide of the linker (linker-primer) and a second, nested, gene-specific primer (primer 2).

This method amplifies all molecules that have undergone complete primer extension and linker-ligation. Electrophoretic separation of the amplified fragments on DNA sequencing gels gives high quality sequence ladders that can be visualized by hybridization with an appropriate probe. The quality of the ladders obtained is the same for genomic mammalian DNA as it is for cloned DNA. In practice, the separated fragments are transferred to a nylon membrane prior to hybridization. This procedure has several advantages, including the allowance for a type of "multiplexing." LMGS will be useful for sequences that are hard to clone, or where directional sequencing is desirable. The project objective is to improve

the chemistry and simplify the procedures for LMGS in the short-term and automate the LMGS technique in the long-term. (RPIS 10442)

BIODE, Inc.

Cape Elizabeth, ME 04107

339. An Acoustic Plate Mode DNA Biosensor

D.J. McAllister

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\$50,000

This project is developing a new solid-state biosensor technology for biological measurements. This technology is based on the merging of two relatively different technologies: nucleic acid probes (DNA hybridization technology) with acoustic plate mode (APM) microsensors. Recent advances in the design and operation of APM devices have demonstrated a DNA hybridization sensor principle with excellent sensitivity (nanograms/milliliter), selectivity, and temperature stability when used with a model probe system. This project is the first attempt at the direct electronic in situ sensing of a diagnostically significant DNA gene sequence, one that codes for the abundant late matrix antigen of cytomegalovirus. This new DNA biosensor operates in a continuous and therefore homogeneous mode and yet is expected to equal or exceed the sensitivity limits of existing dot-blot technologies. Thus, the biosensor is expected to respond, in situ, over time to the target DNA. In contrast, the current technology yields a discrete endpoint result. The biosensor response will be an electronic signal, allowing numerous data handling options. The Phase I project consists of several components: (1) an optimized dual delay line APM sensing element is being constructed; (2) a dual oscillator measurement system for the optimized APM is being designed and constructed; (3) the chemistry employed to covalently attach the nucleic acid probe is being optimized; (4) the performance of the sensor in detecting in situ hybridization of target DNA is being evaluated; and (5) the characterization of the sensor is to be completed.

The overall research is anticipated to provide a novel clinical and diagnostic tool for detecting and quantitating target DNA sequences. The technology is expected to provide a sensing instrument capable of rapid and repeated assays, in situ, of a specific DNA sequence. This technology would have many immediate applications in the areas of health care (both diagnostic and research), forensics, and food processing (i.e., detection of salmonella). (SBIR)

Boston University

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Center for Advanced Research in Biotechnology

340. Overcoming Genome-Mapping Bottlenecks

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\$360,000

The project uses a combination of short- and long-term approaches to eliminate some bottlenecks in current methods of genome mapping. One major thrust is to optimize several potentially improved methods for chromosome fractionation. An ample supply of purified human chromosomes would be a boon to many mapping strategies, including (1) the preparation of large-insert libraries such as yeast artificial chromosomes (YACs), (2) the efficient assignment of many different types of clones to chromosomes or chromosome regions, and (3) the efficient construction and completion of physical maps. A second major focus is to develop efficient top-down strategies for assigning large-insert clones like YACs to chromosome regions and ordering these clones.

Among the major short-term projects are improved magnetic bead-based chromosome separations and improved pulsed-field gel separations of very large DNA pieces. The project is also beginning studies to enhance the generation and fragmentation of very extended chromosomes or DNA molecules and eventually use them to develop efficient methods for assigning YACs to precise chromosome locations. (RPIS 10787)

College of Engineering

341. Physical Structure of Human Chromosome 21

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\$570,000

A complete *Not* I macrorestriction map is being constructed for human chromosome 21. Macrorestriction fragments are fractionated by pulsed-field gel electrophoresis, ordered, and regionally assigned by using hybridization experiments. Genetically mapped sequences used as hybridization probes provide anchor points between the genetic and physical maps. De novo isolated linking clones identify contiguous fragments and are used to regionally assign *Not* I restriction fragments using a panel of hybrid cell lines. Probe hybridization to genomic DNA partially digested with *Not* I provides further information on adjacent fragments.

These approaches have assigned about 80 percent of the *Not* I restriction fragments. End-game strategies focus on chromosome 21 fragments contained in a hybrid cell line (WAV17). Hybridization of human-specific repetitive probes to *Not* I-digested WAV17 DNA revealed a minimum set of chromosome 21 restriction fragments. Single-copy sequences are assigned to the *Alu* fragments by hybridization. Inter-*Alu* polymerase chain reaction was used to generate single-copy

probes from unassigned *Not* I fragments. These probes were used to regionally assign the *Not* I restriction fragments and to identify neighboring fragments. This links unassigned fragments to assigned fragments. The *Not* I map is being used to order chromosome 21 yeast artificial chromosomes by generating inter-*Alu* probes from *Not* I restriction fragments. (RPIS 5644)

University of California, Berkeley

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Chemistry Department

342. Ultrasensitive Fluorescence Detection of DNA

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A.N. Glazer

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\$254,000

Ultrasensitive fluorescence methods, reagents, and apparatus for the detection of labeled DNA are being developed.

A laser-excited confocal fluorescence gel scanner has been developed that provides dramatically improved detection of DNA on gels. This system is being improved by incorporating the ability to detect two or more fluorescent probes simultaneously and by performing multipoint or line-focus scanning that will reduce the scan time.

A technology is being developed for micro DNA-sequencing gels to reduce the electrophoresis time and increase the information density on gels. The initial goal will be to reliably perform sequencing with lanes that are ~1 mm wide with a 15-30 cm lane length. The next goal is to develop new loading techniques that will permit the reduction of the lane width below 1 mm.

Development continues on stable double-stranded DNA-dye complexes that provide a new class of macromolecular assemblies for fluorescence labeling. These dye-DNA complexes can be detected with high sensitivity directly on gels, eliminating the need for staining with large quantities of mutagenic dyes or using radioactive labels followed by autoradiography.

An ultrasensitive stage-scanned confocal fluorescent microscope is being constructed and used to develop new chromosome staining dyes and procedures. This improved sensitivity will be vital as new probes are developed to locate single copy sites such as STSs on chromosomes.

The use of fluorescence-detected capillary electrophoresis is being developed to separate and identify DNA restriction fragments. Methods to permit sequence-specific labeling of DNA fragments separated by capillary electrophoresis are being explored to provide a sensitive new way to identify pathogenic DNA or mutated sequences.

Continuing research investigates methods for single-molecule and single DNA particle fluorescence detection. Fluorescence burst detection is being used to count labeled DNA molecules separated by capillary electrophoresis. Development of single-molecule detection of specifically labeled

fragments separated on capillary electrophoresis will enable ultratrace detection of specific DNA sequences, which will dramatically advance disease and mutation detection. (RPIS 10432)

Electronics Research Laboratory

343. Efficient Algorithms and Data Structures in Support of DNA Mapping and Sequence Analysis

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\$224,000

Research in computational algorithms is being conducted in support of the Human Genome Program. This research concentrates on algorithms for physical map construction, sequence matching and alignment, detection of specific motif patterns in DNA that are biologically significant, and sensitivity analysis for these problems. Researchers are developing practical algorithms for these problems that are faster than existing methods. In particular, these researchers are looking for alternatives for the dynamic programming approach, which has been the method of choice in most applications in molecular biology. (RPIS 10268)

Institute for the Study of Social Change

344. Pathways to Genetic Screening: Patient Knowledge Patient Practices

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D. Beeson

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\$70,000

The near future will witness the screening and counseling of scores of thousands who have had no previous experience with a genetic disorder. This project seeks to illuminate the processes by which genetic screening and genetic concepts of health and illness penetrate two contrasting communities and become integrated into the health concerns of high risk families. The goal is to clarify the cultural frames used to process new genetic information and to explore barriers and bridges to successful genetic intervention.

Because the vast majority of at-risk individuals are not part of clinic populations, this project is designed to reach beyond the clinic into high risk groups that have not yet taken advantage of screening options. The project studies high risk men and women who are in their early reproductive years, compares those who used genetic services with those who have not, and examines their social networks and extended families. It focuses on issues of privacy, stigma, and discrimination as identified in earlier research and looks at how these issues are managed within family and institutional networks. Understandings, interest, and responses are analyzed in two cultural contexts: one in which the disorder is generally recognized as race-linked, and the other in which this association is not part of the popular consciousness. The project is exploring barriers and potential conflicts as they vary by distance from the experience of genetic disorder.

Findings from this study will assist health policymakers in anticipating issues and in preventing the potential adverse effects of new genetic interventions. This assistance will contribute to culturally sensitive genetic screening and counseling that accomplishes medical objectives and responds to privacy concerns and other interests of the patient population. (RPIS 10659)

University of California, Cedars—Sinai Medical Center

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Department of Pediatrics, Medical Genetics

345. Human cDNA Mapping Using Fluorescence In Situ Hybridization

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\$400,000

This research is creating a cDNA map of the human genome. Mapping is approached using the techniques of high resolution fluorescence in situ hybridization (FISH).

The human genome is estimated to consist of some 100,000 genes, up to 30,000 of which may be expressed in the brain. One approach to the rapid identification of these genes has resulted in the cloning and partial sequencing of cDNAs for 337 new genes, 48 similar to genes in other organisms and 30 known genes. The application of these expressed sequence tags to genome mapping and as genetic disease markers is limited by the lack of high resolution information about their positions in the genome.

On the basis of current technology for high resolution mapping of cDNA clones, the project is testing the use of FISH in the rapid mapping of cDNAs to single human chromosome bands.

To discover the inherent limitations to be overcome in a large scale cDNA mapping project, it is necessary to examine a diversity of representative sources of cDNAs; identify desirable and undesirable cDNA characteristics; and determine the resolution, accuracy, sensitivity, and throughput of current methodology. (RPIS 10646)

University of California, San Francisco

San Francisco, CA 94143

Department of Laboratory Medicine

346. Molecular Cytogenetics and Computer-Assisted Microscopy

J. Gray

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\$500,000

This project conducted in collaboration with the Human Genome Center, LBL, improves speed and accuracy in detecting and characterizing cells that carry genetic aberrations by developing fluorescence in situ hybridization (FISH) with physically mapped probes and computer-assisted fluorescence microscopy. To accomplish this goal, a set of nucleic acid markers distributed along each chromosome is being developed

as probes for FISH. The probes are selected to optimize computer-assisted analysis of metaphase spreads and interphase nuclei and contain elements targeted to the rapidly expanding set of genetic loci implicated in human disease. The design and production of such a resource contribute to the human health objectives of the human genome effort.

Key features of the project are (1) primary probes distributed at 2- to 4-Mb intervals along each chromosome for general localization of aberrations. Secondary reagents composed of more closely spaced or overlapping probes may be added as they are developed by the Human Genome Project. This addition will permit more precise definition of an aberration that has been roughly localized using the primary reagent. Initial work is being concentrated on the primary reagent because this reagent can be assembled now with relatively modest effort; (2) differential probe labeling and multicolor analysis instrumentation to allow simultaneous analysis at many loci; (3) probe distribution selected to facilitate automated analysis; (4) probe target size optimized for metaphase and interphase analysis (i.e., ~100 to 400 kb in extent) so the hybridization efficiency is high and the interphase hybridization signal is tightly confined; (5) probes to loci known to be involved in genetic disease included in the set (e.g., probes to 21q22.3, Rb1, erbB-2, c-myc, BCR, and ABL); (6) probes selected, when possible, to contain polymorphic regions so they can be tied to the genetic map and used in loss-of-heterozygosity studies or in linkage analysis.

Physically mapped probes will be obtained from DOE and National Institutes of Health mapping projects when possible. However, many chromosomes are not likely to be well populated by mapped probes in the near future. Investigators intend to cover these regions by multiplex mapping, using probes from chromosome-specific cosmid or yeast artificial chromosome libraries. Each multiplex hybridization maps one clone from each of several libraries. These clones are grown, labeled, and hybridized as a unit. Most metaphase spreads will thus show a single hybridization domain on each of the target chromosomes. The probe locations will be mapped using semiautomated fractional-length analysis.

Much of this process—including multicolor image acquisition, calculation of the chromosome axis, cosmid location, and fractional-length calculation—has already been automated. Addition of automated metaphase findings should yield a system capable of analyzing several multiplex hybridizations per hour, yielding a throughput of ~100 cosmids/d.

Computer-assisted microscopy is being developed to support two aspects of applying the finished probe sets to biological and clinical problems: (1) automated analysis of metaphase chromosomes for aberrations. Proper selection of the hybridization probes should simplify automated analysis by allowing development of a banding pattern with maximum discrimination between chromosomes of similar size and shape; and (2) interphase cytogenetic analysis. Areas to be developed include hybridization domain enumeration to facilitate aneuploidy detection, quantification of gene amplification, and detection of gene loss; detection of rare, genetically aberrant cells (e.g., residual leukemic cells or metastatic cells in the peripheral

blood or bone marrow); and correlated analysis of cellular phenotype (e.g., immunophenotype) and genotype (e.g., FISH signal). (RPIS 10616)

California Institute for Biological Research La Jolla, CA 92037

347. New Hosts and Vectors for Genome Cloning

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P. Greener

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\$259,000

A novel *E. coli* host/vector system for cloning large (250–450 kb) inserts of foreign (archaeobacterial and human) DNAs is being developed to speed mapping of complex genomes. This involves (1) constructing *E. coli* hosts with different combinations of mutations that prevent the rearrangement of DNA inserts with features of highly repetitive human DNAs, including direct and inverted repeats, Z-DNA sequences, (CA)_n, and (A)_n; (2) constructing macron vectors, novel vectors that carry large foreign DNA inserts as invertible segments of single-copy, amplifiable *E. coli* plasmids; (3) testing these and similar cosmid vectors by making ordered-clone maps of archaeobacterial genomes (ca. 2,000 kb in the least complex genomes); and (4) testing these systems by attempting to make an ordered-clone map of human chromosome arm 21q (ca. 40,000 kb). (RPIS 10272)

California Institute of Technology Pasadena, CA 91106

Biology Division

348. Developing a Physical Map of Human Chromosome 22 Using Pulse Alternating Current Electrophoresis and Large Fragment Cloning

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B. Birren

H. Shizuya

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\$525,000

The goal of this project is to derive a set of overlapping clones covering human chromosome 22. Much of the work involves the development of new or improved methods for cloning large DNA fragments and for handling, analyzing, and overlapping these clones. To create an overlapping clone map of human chromosome 22, a set of new bacterial artificial chromosome (BAC) vectors is being developed that should support the cloning of large DNA fragments, about 200 kb in length. These BAC vectors are based on the *E. coli* F-factor and are being constructed to contain promoters for walking, a multiple cloning site, a cos site for cleavage reactions, rare-cutting sites surrounding the insert, and two selectable markers. A library of chromosome 22 is being constructed in these vectors, in modified yeast artificial chromosome vectors, and in cosmids. Source DNA for the libraries comes from hamster/human hybrid cells that contain either intact or deleted chromosome 22. Human

clones are being selected from the libraries by screening with total human DNA. Fingerprints of the clones from the different vector systems are being achieved by partially digesting the cloned DNA and labeling the cos sites with either radioactive or fluorescent tags. The cos sites are being cut with terminase and labeled by a hybridization-ligation reaction. Because each cos end has a different sequence, different oligos can be ligated to each site and a partial-digest map can be created from each end of the clone. The use of fluorescent tags attached by ligation allows the simultaneous use of different fluorochromes at each cos site while separate restriction analysis is being done for radio-labeled oligonucleotides. Detection of the restriction fragments is being performed on the PACE pulsed-field gel electrophoresis system. Based upon the partial digest data, computer algorithms construct the overlap map. (RPIS 10107)

Science and Technology Center

349. Biological Information Signal Processor: Very Large Scale Integration Solutions to Sequence Comparison Problems

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E. Chen (JPL)

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\$480,000

This investigation has focused on redefining the dynamic programming paradigm so that not only can these methods be implemented effectively in silicon, but they can also provide the flexibility required of a robust biological tool. The Biological Information Signal Processor (BISP) represents a systolic implementation of a dynamic programming algorithm based on that of Smith and Waterman, optimizing its ability to define local similarities. Three fundamental functional differences exist between BISP and previous efforts: (1) BISP is optimized for the determination of any number of local similarities between pairs of sequences (although the algorithm is also capable of returning global comparison values). (2) BISP returns values that will allow for the reconstruction of the alignment. (3) BISP is specifically designed to employ complex, user-definable similarity rules. Most significantly, BISP supports user-selectable alphabets of up to 128 characters, complete indel penalty definition, and completely, individually defined similarity values between characters in the chosen character set. (RPIS 9869)

The Catholic University of America

Washington, DC 20064

Department of Biology

350. A Bacteriophage T4 In Vitro DNA Packaging System To Clone Long DNA Molecules

V.B. Rao

V. Joshi

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\$105,000

Bacteriophage T4 packages about 170 kb of its DNA that includes 2 percent terminal redundancy in a strictly headful manner, that is, without genetically preferred ends. The researchers have recently purified the various packaging components of phage T4 and developed an in vitro DNA packaging system. This system is being used to clone foreign DNA of about 150 kb in size, and to construct genomic libraries. The 95 kb *trp* and the 100 kb *Not I* fragments of *E. coli* have been cloned into the P1-*lox* vectors using this system. (The P1-*lox* vectors were developed at DuPont.) The researchers have also generated genomic libraries of *E. coli* DNA from partial BamHI digests. The clones obtained range between 40 kb and 135 kb. The researchers are addressing various aspects of this system, such as isolating large quantities of 150 kb size intact DNA fragments and improving the efficiencies of cloning, etc., in order to construct 150 kb size human genomic libraries. (RPIS 10267)

Cold Spring Harbor Laboratory

Cold Spring Harbor, NY 11724

351. Human Genetics and Genome Analysis: A Practical Workshop for Public Policymakers and Opinion Leaders

J. Witkowski

D.A. Micklos

M. Henderson

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\$65,000

This project involves workshops for nonscientists who are concerned with the societal implications of the information generated from human molecular genetics research. The program seeks to expand the knowledge base of community and public policy leaders to enable more effective analysis of social issues arising from human genome research. Attendees include public policymakers such as congressional staff and state legislators, civic leaders, program officers and planners from health-related foundations, and science journalists, among others. Three-day workshops are offered twice yearly. Participants are selected solely on the basis of their interest or involvement in the Human Genome Project; critics as well as proponents of the practical applications of human molecular genetics data are included in the selection process. The workshops include lectures/discussions on the scientific basis of human genetics and recombinant DNA techniques, an in-depth review of past and future uses of genetic technology, and

opportunities to perform some of the standard experiments in relevant molecular biology. The workshops are held at the Banbury and DNA Learning Centers of Cold Spring Harbor Laboratory. (RPIS 10458)

Division of Computational Biology

352. A Computer System for Access to Distributed Genome Mapping Data

T.G. Marr

A. Reiner

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\$338,000

This project has two goals. One goal is to develop software that accesses multiple databases and retrieves data that contain information useful for accelerating mapping human chromosomes. The software accesses molecular sequence databases (e.g., GenBank, EMBL Data Library, PIR, SwissProt), which contain data required to design oligonucleotides for probing DNA, including primer pairs for polymerase chain reaction (PCR)-based methods.

The other goal is to develop software that qualitatively integrates the following mapping data: (1) markers regionally localized using cytogenetic methods, (2) polymorphic markers ordered by genetic linkage analysis, (3) clones ordered by various "finger-printing" methods, (4) fragments ordered by long range restriction mapping, (5) single genomic fragments or clones that have STSs assigned to them, (6) nucleotide sequences, and (7) the associated metadata such as the submitting investigator's name, location, etc.; the source organism; the chromosome from which the element comes; and the chromosomal location to whatever detail is available. (RPIS 10494)

Collaborative Research, Inc.

Waltham, MA 02154

353. Chimera-Free, High Copy Number Yeast Artificial Chromosome Libraries and Efficient Methods of Analysis

D.T. Moir

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\$300,000

This research defines procedures for generating chimera-free yeast artificial chromosome (YAC) libraries in new vectors that permit facile screening and chromosomal walking. This project is (1) defining YAC cloning methods that minimize the formation of molecules with chimeras or multiple inserts, (2) developing new vectors with amplification capacities and methods that facilitate library screening and manipulation of insert DNA, (3) incorporating these advances and building a large insert YAC library of human DNA equivalent to five genomes, and (4) preparing high density screening blots from the amplified YAC clones in this library for distribution to other laboratories.

The results of this research reveal the role of *in vitro* coligation and *in vivo* recombination mechanisms in generating chimeric YACs and provide methods for minimizing chimera production. Two differently marked YACs or YAC-ligation reactions will be mixed and used to transform wild-type and recombination-deficient host strains carrying auxotrophies for the markers on the YAC arms. Analysis of the marked arms of the resulting YACs by auxotrophic phenotype and Southern blots indicate the frequency of YACs with recombinant arms due to recombinational mechanisms and the effect of recombination-deficient hosts on chimera formation. Coligation frequencies are assessed and reduced by using an excess of oligonucleotide linker/adaptors to saturate the human DNA insert ends before ligation to vector arms. (RPIS 10640)

The Colorado College

Colorado Springs, CO 80903

Biological Sciences Curriculum Study

354. Mapping & Sequencing the Human Genome: Science, Ethics, & Public Policy—Development & Distribution of Educational Materials for Use in High School Biology Classes

J.D. McInerney

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\$184,000

The Biological Sciences Curriculum Study (BSCS), in conjunction with the American Medical Association (AMA), is involved in a 16-month project to develop and distribute a 75-page module entitled "Mapping and Sequencing the Human Genome: Science, Ethics, and Public Policy." The module will consist of background material for teachers (25 pages) and at least 5 instructional activities for the classroom (50 pages). The materials are being designed for use by average students in first-year biology courses (generally taught in 10th grade), with extensions and elaborations appropriate for more advanced students. Approximately 80 percent (some 2.25 million annually) of all high school students in the U.S. take introductory biology.

Module development is a multistep process. The content of the module is first determined by a 10-person project advisory committee that includes experts in science education, classroom teaching, human genetics and molecular biology, ethics, public policy, and computing. In one month, the committee sets the conceptual framework for the module, proposes specific content for the teacher's background material, and suggests instructional activities for the classroom. The summary of this planning meeting is reviewed by the education committees of the American Society of Human Genetics, the National Society of Genetic Counselors, the Council of Regional Networks for Genetic Services, and two independent reviewers (months 2-4). A six-member writing team prepares the background and instructional materials. BSCS and AMA project staff supervise the writers and review all written material (month 5). The experiment is produced during months 6-8, and the program is field tested and

evaluated during months 9-13. The advisory committee reviews the field-test data and makes final recommendations for revision (month 14), and the final revision is completed during months 14-16. The module is distributed free by mail to all 55,000 high school biology teachers in the U.S. (month 16). Upon publication of the program, Ward's Natural Science Establishment, Inc., will become the official supplier of the laboratory and kit materials. (RPIS 10453)

University of Colorado Health Sciences Center

Denver, CO 80206

355. cDNA Sequence-Tagged Site Map of the Human Genome: Methods Development and Applications Using Brain cDNAs

J.M. Sikela

A.S. Khan

A.K. Orpana

A.S. Wilcox

J.A. Hopkins

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\$165,000

This research is contributing to the generation of the detailed cDNA/sequence-tagged site (STS) expression map of the human genome by converting human brain cDNAs to STSs. Ideally, such a map would be composed of a collection of unique cDNAs, each in the form of an STS with a known chromosomal location and, therefore, easily accessible to interested investigators. In addition, each cDNA would be stored in a microtiter plate well and have its own address. Toward this end, this project involves the selection of large numbers of individual cDNAs from directionally cloned human brain libraries that have been prescreened to enrich for unique cDNAs. Partial DNA sequence from each cDNA is being obtained by single-pass, high throughput automated DNA sequencing, using a single sequencing primer for all clones. To identify potential functional relatedness to other genes and to minimize duplication of effort, sequence information for each cDNA is being compared with sequences in internal and external DNA and protein databases. For STS generation, polymerase chain reaction (PCR) primers designed from 3 prime untranslated regions are being used to assign cDNAs to specific chromosomes and chromosomal regions by PCR analysis of somatic cell and, when available, radiation hybrid DNAs. Improvements in the speed and accuracy of these strategies will be investigated. (RPIS 10571)

Department of Biochemistry, Biophysics, and Genetics

356. Chromosome Region-Specific Libraries for Human Genome Analysis

F.-T. Kao

J.-W. Yu

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\$224,000

Molecular analysis and fine structure mapping of the human genome require isolation of large numbers of DNA probes from defined regions of the chromosomes. A direct approach is to use chromosome microdissection to physically remove the chromosomal region of interest and to clone the dissected DNA sequences by microcloning. This project is developing additional expertise in this microtechnology and applying it to the construction of region-specific libraries for human genome analysis.

The specific project objectives are (1) to fully develop the technique of chromosome microdissection and polymerase chain reaction (PCR) microcloning and also to use this technology to provide region-specific libraries as resources for physical mapping of the human genome, (2) to further develop expertise in the PCR microcloning technique using universally amplified DNA sequences from microdissected chromosome fragments by the linker-adaptor method, (3) to develop PCR microcloning by the terminal deoxynucleotidyl transferase method, and (4) to apply this technology to human chromosomes 2 and 5 as models to construct region-specific libraries for these chromosomes and to make the libraries available to Lawrence Livermore National Laboratories and Los Alamos National Laboratory for their physical mapping purposes. If the present pilot efforts prove successful, the long-term goal will be to extend this technology to other human chromosomes and important chromosomal regions, constructing region-specific libraries that permit a more efficient analysis of the human genome. (RPIS 10443)

Columbia University

New York, NY 10032

Department of Genetics and Development

357. Chromosome Specific cDNAs and Sequence-Tagged Sites

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\$407,000

These researchers are participating in the overall effort toward the mapping and sequencing of the human genome by constructing and normalizing cDNA libraries from human tissues, developing methods for the assignment of cDNAs to particular chromosomes and chromosomal regions, and using the assigned cDNAs to generate sequence-tagged sites (STSs). This strategy involves the generation of cDNA libraries using novel vectors (lafmids) constructed and tested by researchers. Following

cDNA cloning in *lambda* phages, single-stranded versions of the libraries can be obtained and used for library normalization by a kinetic approach. Hybridization between normalized and chromosome-specific libraries can then be employed for assignment of cDNAs to chromosomal regions. Both the assigned cDNAs and the corresponding exon-containing genomic clones will be used as sources of STSs. (RPIS 10562)

Columbia University Law School New York, NY 10027

Legislative Drafting Research Fund

358. Lawful Uses of Knowledge from the Human Genome Project

F. Grad

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\$300,000

Lawful Uses of Knowledge from the Human Genome Project, a study of the project's social and legal implications, is being produced by the Legislative Drafting Research Fund.

Part I: The Right to Know or Not To Know about Personal Genomic Information involves the study of available legal protections of these rights of confidentiality. The study examines the rationale for legal protection of information and seeks to balance confidentiality against the value of disclosure for the public or individuals. The risk of discrimination is weighed against the risk of nondisclosure to spouses and other family members, intended spouses, and appropriate government agencies that need information for sound public health planning and other policy purposes. The study discusses whether physicians should be subject to less restriction when information can protect a spouse or other family member.

Part II: The Uses of Genomic Information in Public Health Planning studies the availability of and need to collect such data for planning public health and therapeutic services and for program development. The feasibility of incorporating these findings into legislation to ensure the future flow of information on the prevalence, treatment, and outcome of genetic disease and the development of programs is also being addressed. (RPIS 10641)

Commonwealth Scientific and Industrial Research Organization

359. A Precise, Passive, Narrow-Beam Infrared Filter Radiometer and Its Use with Laser Radar in the Atmospheric Radiation Measurement Program

C.M.R. Platt

(03) 586-7665

Global Change—The objective is to upgrade existing radiometric instrumentation for implementation of the laser radar (LIDAR) Radiometer (LIRAD) method at the Atmospheric Radiation

Measurement (ARM) Southern Great Plains Cloud and Radiation Testbed (CART) site and use the LIRAD method to develop improved parameterizations of cloud radiative effects for incorporation in general circulation models of Earth's climate. This produces a prototype high precision filter radiometer suitable for measuring cloud infrared radiances in the 8- to 13-micron spectral region. The approach is used to construct an infrared filter radiometer with sufficient sensitivity and precision to measure low radiances from thin cirrus clouds at high altitude as well as higher radiances from lower and denser clouds against a background of water vapor emission; install and demonstrate the LIDAR at the first ARM CART site near Lamont, Oklahoma; acquire accurate and precise observations of cirrus cloud downwelling infrared radiance in combination with LIDAR backscatter observations; calculate accurate values, using simultaneously measured temperature and water vapor profiles (e.g., with a balloon-borne sonde), for the cloud emittance and optical depth at several wavelengths in the atmospheric window between 8 and 13 microns; and establish correlations between cloud albedo and cloud infrared radiative properties for parameterization algorithms.

Computational Biosciences, Inc. Ann Arbor, MI 48106

360. High Performance DNA and Protein Sequence Analysis on a Low Cost Parallel Processor Array

J.R. Hartman

(313) 426-9050

\$500,000

As the growth of DNA and protein sequence databases continues to accelerate, exhaustive methods of searching them for homologies and biologically meaningful features have become increasingly impractical on traditional serial-architecture computers. Recently, considerable work has been done to implement these methods on supercomputers and high end massively parallel processors, but the expense and poor accessibility of these machines makes them inaccessible for most molecular biologists. Several efficient algorithms for the exhaustive comparison and homology searching of macromolecular sequence data were implemented on a relatively inexpensive single-instruction, multiple-data-stream, parallel array computer. These algorithms were carefully and rigorously evaluated with respect to their correctness and performance behavior: one in particular was found to offer impressive cost/performance advantages over functionally equivalent serial software. The system as presently configured consists of a Sun SPARCstation 1+ host in addition to the parallel computer, which also includes an MC68020 processor that can be used concurrently. During Phase II, overall system throughput is being maximized using a detailed multiplex optimization strategy designed during Phase I. Also, an X-Window-based graphical user interface following the OpenLook specification is being designed and implemented, and significant new sequence analysis and data management functionality is being developed.

The success of this project will result in the commercial introduction of a parallel processing, sequence analysis work-

station with robust capabilities and unprecedented cost/performance characteristics. The availability of very high performance sequence analysis capabilities at reasonable cost will facilitate a decentralized approach to the Human Genome Project and substantially improve the return realized on research dollars invested. (SBIR)

361. Low Cost Massively Parallel Neurocomputing for Pattern Recognition in Macromolecular Sequences

J.R. Hartman

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\$50,000

Connectionist (neural network) approaches to pattern recognition and analysis have attracted great interest recently because of their flexibility, ability to learn by example, and ability to "self-organize" to reveal hidden patterns and relationships in the input data set. Neural networks are inherently parallel computational structures and thus potentially excellent candidates for implementation on massively parallel computers. Particularly in the training stage, serial implementations of connectionist models are often limited with respect to either the size of a network that may practically be simulated or the number of training trials that is practical. The explosion in the size of macromolecular sequence databases (such as GenBank) that is already occurring has created a need for pattern analysis solutions with cost performance characteristics superior to those currently available. Phase I of the planned research implements efficient parallel algorithms for all critical components of a basic multilayer, feed-forward neural network model. These include a "linear combiner" for the multiplication of connection weight matrices with input (or error) vectors, a sigmoidal activation function to introduce nonlinearity in neuron behavior, and a complete parallel implementation of the back-propagation (generalized Delta rule) training algorithm. Once implemented, the network is being evaluated against alternative parameterizations in a prototype DNA sequence pattern recognition task.

A sequence analysis workstation employing a single instruction multiple data linear array massively parallel processor is being developed. The success of the planned research will result in the addition of powerful, flexible, and high performance pattern recognition and analysis capabilities to this platform. (SBIR)

The University of Connecticut
Storrs, CT 06269

Department of Molecular and Cell Biology

362. A Probe-Based Mapping Strategy for DNA Sequencing with Mobile Primers

L.D. Strausbaugh

C.M. Berg

(203) 486-2693

\$282,000

A major challenge to most sequencing strategies is the fractionation of large DNA segments into smaller ones appropriate for

sequencing. In many currently employed strategies, small random subclones are generated in specialized vectors and the DNA sequences obtained from these collections are ordered by computers; such random approaches have the disadvantages of numerous *in vivo* manipulations, the unavoidable repeated sequencing of the same fragments, and requirements for extensive computer time. In this project, transposon-based strategies have been developed that simultaneously provide effective answers to the problems of subdivision of large cloned inserts and the lack of ordered primer binding sites. The movement of a transposon to a new site results in the introduction of a specific DNA sequence at that site; thus, transposons can be engineered to become mobile vehicles for the delivery of a DNA sequence to numerous sites in the cloned target DNA. These introduced sites permit sequencing or polymerase chain reaction (PCR) amplification of the target DNA from only a small number of primers, substantially reducing the costs of such procedures.

A prerequisite for the use of a bacterial transposon as a delivery vector for primer binding sites is that the insertions occur essentially at random. Furthermore, ease of manipulation is essential for the widespread adoption of a transposon-based system. We have concentrated on developing derivatives of gamma delta, judged the best transposon available with respect to these desirable properties. We have reduced to practice the use of gamma delta to provide mobile primer binding sites for both large (up to 19 kb) and small plasmid molecules. The mutagenesis protocols and selections have been streamlined for maximum ease and adaptability. It has been shown that gamma delta transposes randomly and efficiently into many sites in cloned prokaryotic and eukaryotic fragments, even in ones with regions of highly nonrandom base composition. Using a simple probe-mapping procedure, the location and orientation of transposon insertions are easily determined; the subsequent selection of insertions for sequencing converts DNA sequence acquisition to a highly nonrandom form. The use of gamma delta derivatives and probe mapping in the study of large fragments cloned in cosmids is currently being perfected; successful completion of this project will render transposon-based approaches available for existing cosmid libraries. We are also examining the utility of gamma delta as a tool in the analysis of even larger eukaryotic fragments cloned in vectors based on P1. In these experiments, we will use "crossover" PCR mapping and linear amplification sequencing.

One of the most powerful applications of transposon-based approaches is the ease of adaptation to new sequencing strategies. For example, we have constructed "multiplex" gamma delta transposons that contain the Milligen/Biosearch subset of multiplex tags of Church and Kieffer-Higgins. The multiplex tags have been used to map the location and orientation of transposon-borne primer sites in a mixture of DNAs by serial hybridizations. The same probes used in localization are also used in sequencing. (RPIS 10275)

Duke University **Durham, NC 27706**

Department of Chemistry

363. Preparation of Oligonucleotide Arrays for Hybridization Studies

M.C. Pirrung
(919) 660-1556

\$205,000

The long-term goal of this research is to provide all the chemistry needed to prepare complete miniaturized arrays of decanucleotides [4^{10} or 10^6 oligonucleotides (1 million)]. Such arrays can be used in a variety of techniques in molecular biology and medicine, including mapping clones in large genomic libraries, sequencing (DNA) larger than a kilobase by hybridization, and diagnosing diseases via DNA probes.

Very Large Scale Immobilized Polymer Synthesis (VLSIPS, Affymax Technologies N.V.), the technique best suited to preparing sequence arrays, is being used. VLSIPS relies on standard polymer synthesis techniques modified by the addition of a photoremovable group. This project therefore aims first at developing such protecting groups for nucleotides and nucleosides, groups that must have very specific properties that are optimized for the particular polymer synthesis method used. These properties include wavelength of deprotection, extinction coefficient, quantum yield, byproducts, chemical yield, and rate of deprotection.

The value of different supports in both the synthesis and hybridization steps is also being investigated. By standard nonphotochemical means, arrays of oligonucleotides prepared are on rigid and nonrigid supports and supplied to groups around the world that are developing oligonucleotide hybridization as a tool for studying the human genome. Finally, optimal supports, chemistry, and photoremovable groups are combined to permit the synthesis of large oligonucleotide arrays. (RPIS 10623)

Eunice Kennedy Shriver Center for Mental Retardation

Waltham, MA 02254

Division of Medical Genetics

364. Studies of Genetic Discrimination

M. Natowicz
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\$150,000

This study assesses the significance in our society of discrimination directed against individuals and family members because of real or perceived differences in their genetic constitution. Few studies have been done, and limited data exist regarding this issue. Preliminary study indicated that genetic discrimination does occur, and it may have a significant effect on the lives of affected people.

The specific aims of the study are to (1) determine the particular entities, such as insurance companies, government agencies, employers, educational institutions, and the military, that might engage in discriminatory practices and (2) evaluate the nature of the discrimination and determine the underlying basis for it. This study is predicated on learning whether this discrimination is the result of ignorance or of systematic policy.

This study uses a case history analysis of discriminatory practices against individuals and families in the areas listed. Questionnaires are distributed to persons who have been or are at risk for certain single-gene disorders and to asymptomatic heterozygotes for other conditions; detailed follow-up interviews are conducted when appropriate. Specific disorders were selected for the following reasons: (1) the genetic basis of the chosen conditions is well established; (2) the chosen conditions are not associated with disfigurement or disability, so discrimination would most likely be based on genetic concerns; and (3) individuals with these disorders can easily be contacted through existing support groups.

Genetic information and techniques discovered through the Human Genome project raise difficult and important ethical and social policy issues. The successful completion of this study will provide substantial new data regarding the little-studied problem of genetic discrimination. (RPIS 10648)

365. Genetic Data and Privacy: A Search for Model Legislation

P. Reilly

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\$100,000

The Human Genome project holds enormous promise for scientific and medical progress. However, the public is largely unprepared for the anticipated avalanche of new genetic information and its myriad applications. At present there are no safeguards to discourage injudicious applications. Therefore, a public policy must be formulated which will maximize the benefits and minimize the risks of this project.

The purposes of the project are three-fold: (1) to conduct a thorough survey of existing state and Federal legislation (and selected local laws) in order to identify statutes and ordinances that attempt to establish a zone of genetic privacy or that could reasonably be interpreted by a judge to be so intended, (2) to survey the 50 state legislatures to identify, compile, and analyze all bills that purport to regulate access to or use genetic data, and (3) to survey major insurers and state insurance commissioners concerning their views of the need to use genetic information and the need to protect it from abuse. (RPIS 10573)

Florida State University Tallahassee, FL 32306

Supercomputer Computations Research Institute

366. Multiple Alignment and Homolog Sequence Database Compilation

H.A. Lim

(904) 644-1010

\$95,000

In the last few years, and especially after the prolific growth of sequence data since the beginning of the human genome initiative, the problem of sequence alignment has been one of the main subjects of research in theoretical and computational molecular biology. But although different algorithms have been forwarded, they are all based on very simple evolutionary models. The underlying evolutionary mechanisms are not studied in detail and as a result, they are not adequately taken into account in existing alignment algorithms. Most of the efforts have been concentrated on improving accuracy and speed, but the objective function has never been under careful consideration. The first goal of this project is to develop an alignment procedure capable of perceiving and taking into account features of evolutionary patterns for querying sequence samples. To achieve this, the following approaches are being pursued: (1) the alignment of sequence families contained in databases, (2) the study of various alignment parameter values and evolutionary models, (3) and the alignment of computer simulated sequences. This study should also improve the understanding of mechanisms of sequence evolution. The statistically based approach of diagonal fragment analysis is used as a basic alignment technique in this investigation.

The second goal is to compile probable sequence families in a homolog sequence database that will be useful in various applications. To this end, a massively parallel machine such as the Connection Machine allows the investigators to perform the task within a reasonable time.

The third goal of this project is the application of databases developed for human genome sequence investigations. This includes investigations of human multigene families and comparative analysis of human sequences with other species. This should lead to a better characterization of their functional roles. (RPIS 10754)

Harvard Medical School Boston, MA 02115

Department of Biological Chemistry and Molecular Pharmacology

367. Thioredoxin-Gene 5 Protein Interactions: Processivity of Bacteriophage T7 DNA Polymerase

J. Himawan

S. Tabor

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\$424,000

Bacteriophage T7 encodes its own DNA polymerase, the product of gene 5. The 80 kDa gene 5 protein has low processivity, dissociating from a primer-template after incorporating only a few nucleotides. Thioredoxin, a 12 kDa protein encoded by the *E. coli* *trxA* gene, binds tightly to the gene 5 protein in a 1:1 stoichiometry and confers a high degree of processivity by increasing the affinity of gene 5 protein for a primer-template. These researchers have been investigating the host thioredoxin-T7 gene 5 protein interaction by biochemical and genetic methods. The activities of several mutant thioredoxins have been analyzed, identifying amino acid substitutions that modify activity. A host thioredoxin mutant cannot support the growth of wild-type T7 phage. Researchers isolated T7 mutants (revertants) that can grow within the thioredoxin-deficient host. Every T7 revertant contains a mutation within gene 5. Presumably, these mutant gene 5 proteins can compensate for the defect created by the gly-74 to asp-74 alteration in host thioredoxin and can interact productively with the asp-74 thioredoxin mutant to form a DNA polymerase that can efficiently replicate the phage genome. Specifically, the gly-74 to asp-74 mutation in the thioredoxin gene is suppressed by a replacement of glu-319 in the gene 5 protein to either a valine or lysine residue. Genetic and physical evidence suggests that gly-74 of thioredoxin and glu-319 of gene 5 protein represent a contact point between the two proteins. More specifically, the researchers speculate that the side groups of these two amino acids are physically adjacent to one another. The large Klenow fragment of *E. coli* DNA polymerase I and T7 gene 5 protein show extensive homologies. The researchers thus speculate that thioredoxin binds gene 5 protein at the edge of this crevice such that the two proteins together lock or clamp the duplex DNA into position. (RPIS 9855)

Department of Genetics

368. Developing a Fully Integrated Technology for Sequencing Genomes as Large as Those of Humans

G.M. Church

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\$326,000

To develop a fully integrated technology for sequencing genomes as large as those of humans, this study is initially completing small, highly informative genomes, emphasizing techniques which can be generalized to larger ones. The

complete sequencing of small genomes from the most thoroughly studied and genetically useful organisms, *Escherichia coli* (4.7 Mb) and *Saccharomyces cerevisiae* (15 Mb), allows a best fit alignment of corresponding genes among the microbes and provides a database valuable for analysis of larger genomes.

The technology development is driven by the potential contribution to the complete sequencing of eubacterial, archaeobacterial, and eukaryotic genomes in order to determine the basic components of life in the three kingdoms. The research focuses on two areas: (1) Multiplex sequencing, computer-assisted film reading, and interactions among individual steps are being optimized. This entails the developing of methods to combine and compare automatic base assignment and studying the effects of systematically changing laboratory protocols and base assignment algorithms on the final accuracy. (2) Multiplexed directed sequencing strategies including oligonucleotide walking and hybridization selection methods are being developed. The technologies are being developed and tested by the challenge of high throughput sequencing of portions of *E. coli* genomes and related microbial DNA and protein sequences. (RPIS 9722)

The Institute for Genomic Research Gaithersburg, MD 20878

369. Identification of Genes in Anonymous DNA Sequences

C.A. Fields

C.A. Soderlund

(301) 869-9056

\$122,000

The gm system predicts the exon-intron organization of genes from genomic DNA sequence data and displays the resulting exon maps and predicted amino-acid sequences via a graphic user interface. The system is designed to support incremental, exploratory analysis of new sequences as they are obtained, and it is intended for use as a laboratory tool. Gm is written in C, with the graphics interface in X-windows, and it runs on a wide variety of Unix machines. The software has been distributed to several dozen user sites, including major DOE and National Institutes of Health laboratories, which have provided feedback on the utility of the system for analyzing DNA from a number of organisms. Project researchers have tested gm, version 1 on sequences of known genes from *C. elegans*, using gm to analyze new sequences obtained by collaborators. The researchers are designing and implementing new functions. The new release, gm version 2.0, includes six new functions: (1) Partial 3'-end cDNA data can be used to initiate construction of exon maps. This allows maps consistent with a partial cDNA to be examined either alone or together with all other possible maps. (2) Repetitive elements are required to be continued in either introns or intergenic regions. (3) Two- and three-dimensional Markov matrix analyses are used to measure single, di-, and trinucleotide compositions of introns and exons. (4) Predicted exon maps are now ranked in order of increasing protein-coding capacity. (5) Functions for displaying microrestriction maps,

sequence-tagged sites, cDNAs, and repetitive DNA elements at the same scale as the predicted exon maps have been added to the graphic interface. (6) The graphic interface supports multiple system runs with different parameter settings. This facilitates use of gm as an exploratory analysis tool. It also allows gm to serve as an interface for displaying exon maps of known genes together with cDNA and physical mapping data. The interactive menu tool can also be accessed directly from the graphic interface. Menu now includes a function that builds exon maps from known exon coordinates. Current efforts are focused on developing functions to allow use of arbitrary cDNA data to initiate exon map construction and on developing and testing methods for dealing with sequencing errors. (RPIS 10085)

370. Expressed Sequence Tags from Human Brain cDNAs for Genome Mapping

J.C. Venter

M. Adams

M. Dubnick

C. Fields

J. Kelley

A. Kerlavage

R. Moreno

J. Nagle

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\$479,000

Large scale cDNA sequencing and mapping offer unique opportunities for understanding the structure of the human genome and gene expression. The human brain is estimated to contain 20,000–30,000 unique messenger ribonucleic acid (mRNA) species, which represent one-third to one-half of all human genes. Using automated DNA sequencing technology now makes initial characterization of large numbers of cDNA clones possible. This study focuses on construction and analysis of directionally cloned cDNA libraries and automated DNA sequencing of 3' untranslated sequences for the purpose of mapping. Efforts are being made to screen the brain libraries prior to sequencing and to eliminate redundant clones by a combination of approaches, including normalization, subtraction, and differential hybridization. As the project progresses, these researchers will continue to identify unique clones and hope to describe at least 4,000 new expressed sequence tags (ESTs) per year. As pools of clones for subtraction and hybridization screening are developed, they will be made available to other researchers in the field. In addition, sequences will be given to any researcher who desires to perform physical or genetic mapping of ESTs. In preliminary studies, sequence data have been collected from more than 600 human brain cDNA clones. These sequences have proven valuable in several ways: (1) many have shown significant similarity to genes from other organisms, providing a clue to the function of the human gene; (2) more than 40 have been localized to chromosomes using polymerase chain reaction (PCR) screening of somatic-cell hybrid DNA panels, generating sequence-tagged sites for mapping of human chromosomes;

and (3) these sequences will eventually be used to confirm coding regions in genomic sequence and to further our understanding of the expressed gene complement of the brain. Support for the study originated while the group was at the National Institute of Neurological Disorders and Stroke at the National Institutes of Health. (RPIS 10770)

Intelligenetics Inc
Mountain View, CA 94040

371. The BIOSCI Electronic Newsgroup Network for the Biological Sciences

D. Kristofferson

E. Leon

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\$78,000

The Biological Sciences (BIOSCI) electronic newsgroup network serves as an important vehicle for communications among members of the international biological sciences community. This project, cofunded with the National Science Foundation, continues and extends the services provided by BIOSCI. In addition to forums for communications in specialized scientific fields, these services include newsgroups for experimental methods, scientific meetings and other general announcements, job opportunities, journal contents/abstracts, and funding agency announcements. Newsgroups dedicated to various aspects of the Human Genome Project are also in use. Electronic newsgroups have the potential to revolutionize communications among scientists, and their use will be actively promoted among the biological community through demonstrations, training sessions, and assistance with the installation of news software. Prominent scientists are recruited as editors/moderators of some electronic forums. Archives of bulletins are maintained for retrieval by file transfer protocol (FTP) and electronic mail. A database of all newsgroups dedicated to the biological sciences is maintained along with a directory of electronic mail addresses of biological scientists. (RPIS 10760)

Johns Hopkins University School of Medicine

Baltimore, MD 21205

372. A Human Genome Database

P.L. Pearson

R.J. Robbins

N.W. Matheson

V.A. McKusick

C. Francomano

(410) 955-7058

\$2,971,000

The Genome Database (GDB) stores and distributes nonsequence data relevant to the Human Genome Project. Included in the database are information about human genetic loci (and their polymorphisms, alleles, and allele frequencies), probes and other reagents (such as yeast artificial chromosomes, cosmids, sequence-tagged sites, and polymerase chain reaction primer

sets), maps (genetic and physical), clinical disorders, citations (including abstracts), and contacts (names, addresses, telephone numbers, and electronic mail addresses).

The ability to store varied map data and to compare and integrate different maps forms the intellectual focus of GDB within the genome community for the coming years. Because GDB "publishes" both individually authored maps and consensus maps for each chromosome, GDB contains many maps and map fragments for each chromosome.

The GDB program is divided into three core activities: (1) the Administration Core provides general financial and policymaking support and coordinates external advisory group activities; (2) the Informatics Core consists of three sections—product development, computing and network services, and product services; and (3) the Data Acquisition Core maintains three editorial levels—a central support group, a group of five core editors, and 50 editors (located worldwide) responsible for maintaining information on individual chromosomes.

GDB is also divided into two research projects: (1) the Map Integration Project, which develops tools for storing, retrieving, and manipulating map information; and (2) the Online Mendelian Inheritance in Man Integration Project, which restructures genetic disease information to make it more easily accessible to the scientific community. (RPIS 10550)

University of Kansas Medical Center
Kansas City, KS 66103

Department of Medical Genetics

373. Human Genetics Education for Middle and Secondary Science Teachers

D.L. Collins

R.N. Schimke

L. Segebrecht

(913) 588-6043

\$200,000

This study addresses the lack of public information about the Human Genome Project and enhances understanding of the project's social, legal, and ethical issues through educational workshops for science teachers. Identifying genes that cause disease and susceptibility to disease will greatly increase the knowledge necessary for adequately teaching the science student in the 1990s. A working understanding of the implications of the Human Genome Project will be required, not only for the sake of pure science but for the social, ethical, and legal issues surrounding the deluge of new information.

The University of Kansas Medical Center, in conjunction with area science teachers, Science Pioneers (a local nonprofit organization to promote science education), the Midwest Bioethics Center, and voluntary genetics organizations, is conducting a 3-year, four-phase national program to prepare selected science teachers to become state resource teachers. Teacher participants are recruited from public, parochial, private, and special schools (such as those for visually or hearing

impaired). Resource teachers (50 per year for 3 years) are chosen for their knowledge, experience, and links with existing teacher organizations.

Using an inquiry orientation and hands-on materials, participants in a series of workshops update and expand the use of human genetics curriculum materials. These workshops involve clinical geneticists and genetics counselors certified by the American Board of Medical Genetics as well as individuals with genetic conditions. Discussions include the social, legal, and ethical implications of the Human Genome Project. (RPIS 10647)

Large Scale Biology Corporation Rockville, MD 20850

- 374. Instrumentation for Automated Colony Processing**
N.G. Anderson
(301) 424-5989 \$500,000 (2-year funding)

The objective of this project is to develop a 70-mm film strip technology that can be used to clone very large numbers of phage, bacterial, or yeast cells; locate clones and plaques by electronic scanning; identify positive (non-blue) clones (where this technique applies); transfer and reposition clones in large rectangular arrays on a secondary 70-mm film strip; and transfer the entire array to 70-mm strips of nitrocellulose, nylon, or polyvinylidene difluoride. The technology also enables these latter strips to be processed to lyse cells or phage, attach the released DNA to the strips, probe the arrays en masse with DNA probes under different stringency conditions, locate those clones to which the probes hybridize, and identify and order overlapping clones. Methods and a machine have been developed to attach porous spacer strips to 100-foot-long perforated film and filter strips, which allow these to be wound in reels without contact between surfaces. Also developed were a method for causing agar gels to adhere to the film and a machine that allows (1) a gel to be cast along the entire film length and (2) cells or phage to be applied evenly over the entire length. The system is designed to interface with a film-strip-based mass sample storage system and a new polymerase chain reaction (PCR) machine now under development. The system is designed to clone more than 10^6 colonies or plaques automatically, do large matrix hybridization analyses at different and closely controlled stringencies, and recover filter material for multiple reprobing. Key elements of the system are positive clone identification and storage, and arrangements for producing duplicate sets of large arrays. The system is being designed to run automatically in a remote environment under sterile conditions.

This automated colony processing and hybridization system together with the matching film-based storage system, PCR system, and multiple-parallel oligonucleotide synthesis system will form the key large-scale systems that help make completion of the genome project feasible. It is anticipated that these will come into general international use and be the basis for a commercially successful enterprise. (SBIR)

The Library of Congress Washington, DC 20540

Office of the Librarian

- 375. Pilot Resident Fellow Program in Science and Technology: Bioethics Issues in Molecular Genetics**
D.C. Murphy
(202) 707-2443 \$60,000

The Library of Congress is establishing, on a pilot basis, a Senior Resident Fellowship in Science and Technology to explore some of the bioethical issues associated with human genome research. The selected resident fellow conducts a critical review of the existing bioethics literature relevant to molecular genetics, conducts interviews with major groups and researchers involved in relevant bioethical research, analyzes social and ethical issues pertinent to human genome research, and produces scholarly writings and oral presentations to make the findings public. At the end of the year, the fellow submits a review article for publication describing the findings. Other publications are prepared as well. The fellow also prepares one or two public lectures on the research carried out in order to educate interested individuals, including congressional staff. (RPIS 10733)

Linus Pauling Institute of Science and Medicine Palo Alto, CA 94306

- 376. Efficient Identification and Analysis of Low and Medium Frequency Repeats**
J. Jurka
(415) 327-4064 \$90,000

Understanding biology of repetitive elements is becoming a very practical issue for genomic studies. The rapidly growing databases of sequenced DNA present researchers with unprecedented opportunities to pose and address complex questions about repetitive sequences as more sequencing is done. Well-organized databases of repetitive DNA and adequate tools for computer-assisted analyses are needed to pursue these opportunities.

The specific goals of this project are to (1) organize and maintain databases of repetitive elements from primates, (2) develop an algorithm for rapid identification and extraction of novel low and medium reiteration frequency sequences (LOR and MER sequences) from the available sequence data, (3) find and characterize novel primate LOR and MER sequences in the existing databases, (4) generate probes for the identified repeats using the polymerase chain reaction and estimate the numbers of the repeats in the human genome by Southern blotting, and (5) expand the analysis on nonprimate DNA.

Several probes for LOR and MER sequences identified by the above approach are currently distributed commercially for mapping purposes. (RPIS 10454)

Massachusetts Institute of Technology Cambridge, MA 02139

Department of Biology

377. Robust Detailed Mapping of the Human Genome

L.S. Lerman

N. Gabra

E. Schmitt

N.B. Hecht

(617) 253-6658

\$185,000

This project continues a recently initiated effort to develop a new approach to human genomic mapping. The map topography is defined by domains that reflect the local stability of the double helix toward denaturation and equilibrium, with domains both of low and high stability serving as markers. Neither cloning nor restriction endonuclease digestion is required for the method. It is expected that these maps will be substantially more informative than restriction maps, less subject to confusion from minor sequence variations, and capable of indicating similarities between genes and perhaps between related species. (RPIS 10643)

University of Michigan Ann Arbor, MI 48109

Department of Chemistry

378. Scanning Molecular Exciton Microscopy: A New Approach to Gene Sequencing

R. Kopelman

J. Langmore

V. Makarov

B. Orr

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\$245,000

Molecular Exciton Microscopy (MEM) is a new principle of imaging, based on short range optical interactions between a specimen and a microscopic optical probe that is scanned over the surface of the specimen. The microscope depends on the well-understood mechanics of other scanned-tip microscopies such as scanning tunneling microscopy, but is designed to take advantage of the many well-understood optical interactions that occur between molecules separated by 0.1 to 5 nm. Previously, photon-emitting tips have been produced using glass capillaries drawn to small dimensions. Such tips are severely limited due to the difficulty in transmitting photons through subwavelength apertures of the capillaries. These researchers' recent developments have overcome these intensity problems by using excitons. A small exciton-conducting organic or inorganic crystal is grown in the aperture region and illuminated with laser light. The energy, in the form of excitons, is conducted through the crystal to the tip of the microcapillary. The energy is converted again to light, forming an extremely small, bright source of light. The interest of these researchers, however, is to

take advantage of nonradiative interactions between molecules on the tip of the capillary and those on the specimen. The simplest specimens are individual molecules bound to atomically smooth substrates. As the tip is scanned along a flat surface parallel to the substrate, the optical interactions between the tip and the specimen will be detected. The resolution of the microscope is limited by the size of the optical source (dependent upon the geometry of the donor molecule or molecules at the tip), the distance between the source and the specimen (≥ 0.2 nm), and the range of the optical interaction. One interaction useful for low resolution would be Forster-Dexter energy transfer, which would change in the intensity and wavelength of photons emitted from both the tip and the sample. A much higher resolution interaction would be spin-orbit coupling between specific molecules bound to the tip of the capillary and heavy atoms in the sample (known in molecular optics as the "external heavy atom effect"). In principle, the interaction has a range of less than ~ 0.5 nm and is very effective at stimulating emission of light at a new wavelength. Photomultipliers placed above or below the specimen detect specific emissions signals, which are stored on a computer.

MEM offers many possibilities for improving gene mapping and sequencing techniques. If single-stranded DNA with mercury atoms on specific bases can be bound to flat surfaces, the "external heavy atom effect" could be used to localize the heavy atoms to high resolution in order to "read" specific bases along the strands. Use of fluorescent end-labels and intelligent scanning algorithms might allow the labeled bases to be mapped at high speed. These and other optical interactions could be exploited in order to extend the usefulness of optical interaction to near-atomic resolution in a number of potential applications to molecular and cell biology. (RPIS 10254)

Molecular Dynamics Sunnyvale, CA 94086

379. Rapid, High Throughput DNA Sequencing Using Confocal Fluorescence Imaging of Capillary Arrays

D.L. Barker

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\$50,000

The goals of the Human Genome Project require techniques for DNA sequencing that increase throughput over current methods by an order of magnitude or more. Current automated fluorescence sequencing instruments require 5 to 10 hours for a single gel run and accommodate a maximum of 36 reaction sets. Capillary gels can be run at higher voltages to yield separation of 300–500 bases in 1–2 hours, but current fluorescence detection methods are limited to analyzing 1 capillary at a time. Confocal fluorescence imaging has the capacity to produce great sensitivity to detection, with the geometrical advantage that excitation light is delivered through the same lens that collects fluorescence emission. It has recently been shown that a single scanning confocal fluorescence detector can detect DNA fragments in a parallel array of capillaries. The feasibility of this

technology is being tested in the Phase I project for high throughput DNA sequencing, including automated methods to load and analyze up to 200 reaction sets simultaneously in 1-2 hours.

Results should demonstrate the feasibility of developing a cost-effective commercial instrument for high throughput DNA sequencing. This instrument would advance the goals of the Human Genome Project and could also become the method of choice for the hundreds of academic, government, and biotechnology labs performing DNA sequencing. (SBIR)

Morehouse School of Medicine

Atlanta, GA 30310

Department of Pharmacology and Toxicology

380. Impact of Technology Derived from the Human Genome Project on Genetic Testing, Screening, and Counseling: Cultural, Ethical, and Legal Issues

R.W. Trotter

L.A. Crandall

D. Phoenix

M. Imara

R.E. Moseley

(404) 752-1711

\$136,000

This research project explores a variety of complex and interrelated issues involving differences among state-supported genetic testing, screening, and counseling programs, with particular concentration on Georgia and Florida. It assesses factors that influence legislation determining which conditions require mandatory screening. The project also examines the potential implications and impact of genetic screening policy variations on a mobile society of broad ethnic diversity. It addresses issues of access and availability of genetic services in various locales, the nature of counseling provided through the state programs, and the preparation and training of counselors. The project explores the extent to which genetic counselors, nationally certified or not, are trained in the field of counseling and in the science and medicine of genetics. Of particular importance to this research is the core essence of confidentiality of genetic information. (RPIS 10674)

National Academy of Sciences Institute of Medicine

Washington, DC 20418

Division of Health Sciences Policy

381. Predicting Future Disease: Issues in the Development, Application, and Use of Tests for Genetic Disorders

R.E. Bulger

(202) 334-2329

\$175,000

Through its Board on Health Sciences Policy, the Institute of Medicine has established a panel of experts to evaluate issues related to the development, application, and use of tests for

genetic disorders. The 27-month study addresses a variety of issues presented by the rapid proliferation of genetic tests capable of predicting future disease in otherwise healthy individuals. This study attempts to develop responsible approaches to resolving current and future problems presented by the rapid application of genetic tests. In particular, the study focuses on the following areas: (1) the availability of adequately trained personnel to administer and interpret tests; (2) quality control and integrity in testing and approval for wide scale use of tests for single gene disorders; (3) cost-effectiveness of testing; (4) access to test results, specifically by insurers; and (5) the ethical dilemmas related to the issues of autonomy and privacy.

A 20-member committee with expertise in human genetics, law, health education, economics, ethics, medicine, insurance, psychology, and regulation has been appointed to conduct the study. Two workshops have been convened to discuss those topics listed above deemed most important by the sponsoring agencies, and proceedings of the workshops are being disseminated. In addition, a comprehensive report including findings and recommendations will be delivered at the end of the 27-month study. This report is anticipated to reach a wide audience ranging from Government agencies responsible for research funding, regulation, and reimbursement for genetic tests; commercial developers of tests; Congress; State legislatures; medical educators; and disease-specific foundations and advocacy groups. (RPIS 10423)

National Institutes of Health

Bethesda, MD 20892

National Institute of General Medical Sciences

382. GenBank: The Genetic Sequence Data Bank

J. Cassett

(301) 594-7800

\$30,000

The Genetic Sequence Data Bank (GenBank) is an internationally available repository of all reported nucleotide sequences 50 nucleotides or longer that have been annotated for sites of biological interest. GenBank is connected to a similar databank at the European Molecular Biology Laboratory in Heidelberg and to the DNA Database of Japan in Mishima; the three groups share responsibility for collecting sequences worldwide.

This resource is administered by the National Institutes of Health and cosponsored by DOE. The databank is operated under contract to a company that provides overall management, distribution, and user-support services. The Los Alamos National Laboratory collects, enters, verifies, and annotates the sequences. GenBank data are available both online (by modem) and as computer-readable magnetic tape. (RPIS 10117)

National Institutes of Mental Health Washington, DC 20032

St. Elizabeth's Hospital, Neuroscience Center

383. Chromosomal Localization of Brain cDNAs

M.H. Polymeropoulos

(202) 373-6077

\$201,000

The long-term goal of this project is to establish the chromosomal location for 1,600 genes expressed in the human brain and develop strategies to increase the throughput for cDNA mapping. An estimated 50,000 to 100,000 genes are expressed in the human organism. Of these, 30,000 are expressed in the human brain, and about 20,000 are believed to be brain specific. So far, approximately 2,000 genes have been mapped, reflecting only a small proportion of the total number of expressed genes. With the advent of automated sequencing, several hundred brain cDNAs have been sequenced in an effort to obtain partial sequences of the genes expressed in the human brain.

Initially, this research plans to establish a chromosomal assignment for 1,600 of these cDNAs in a manner that provides a direct link with other efforts already under way to develop a physical map of the human genome. This approach sets up chromosomal location of the cDNAs in the following manner: develop a sequence-tagged site (STS) for each sequenced brain cDNA, and determine the chromosomal location for such an STS by the analysis for the segregation of the amplified products in two human-rodent somatic cell hybrid panels.

Based on the establishment of STS for the mapping of the cDNAs, this mapping approach can be fully integrated in ongoing mapping efforts for the mapping of the human genome by providing easily identifiable landmarks based on the DNA sequence itself. Furthermore, the mapping of brain-derived cDNAs will facilitate the identification of genes involved in inherited disorders of the central nervous system, by providing candidate genes in areas where linkage has already been established or is being pursued. (RPIS 5645)

University of Medicine and Dentistry of New Jersey

Newark, NJ 07103

New Jersey Medical School

384. Monochromosomal Hybrids for the Analysis of the Human Genome

R.S. Athwal

(201) 456-5215

\$300,000

The objective of this project is to produce a panel of rodent-human hybrid cell lines, each containing a single different human chromosome (monochromosomal hybrids) marked with an *Ecogpt* gene. The presence of the *Ecogpt* gene affords stable retention of the human chromosomes by allowing their selection

in a medium containing mycophenolic acid and xanthine (MX medium). These hybrid panels provide an invaluable resource for genome fractionation and physical mapping of human chromosomes. In addition, these hybrids are useful in the genetic analysis of complex phenotypes, such as growth regulation in tumor cells and repair of radiation-induced DNA damage.

The experimental approach for producing these hybrids involves "tagging" of the chromosomes in normal diploid human cells by retroviral vector-mediated transfer of the *Ecogpt* gene. Because a transferred gene can integrate at random in the recipient genome, independent gene transfer clones may each carry the selectable marker integrated into a different site and perhaps a different chromosome. The researchers have already produced 153 independent gene transfer clones, now being analyzed for the identity of *Ecogpt*-marked chromosomes. A marked chromosome in human cells is identified by cloning the human DNA, flanking the site of vector integration by polymerase chain reaction amplification, and then mapping the cloned DNA fragment to a specific chromosome. Cell lines for 5 chromosomes have already been identified through this approach, and the ultimate goal is to generate a bank of 24 human cell lines, each carrying *Ecogpt* integrated into a different chromosome.

Normal human cells have a limited lifespan. To perpetuate the marked chromosomes, these cells must be fused with immortalized human tumor cells. To facilitate the transfer of single chromosomes to recipient cells by microcell fusion, human hybrid cells are fused with mouse A9 cells to generate mouse-human segregating hybrids. Mouse-human hybrid cells are used as microcell donors to transfer the marked human chromosome to mouse or Chinese hamster cells. Microcell hybrids isolated by selection in MX medium are analyzed to confirm the identity and integrity of the transferred chromosome. The ultimate objective of this project is to generate two sets of monochromosomal hybrids, one in mouse and the other in Chinese hamster cells. The researchers have already produced monochromosomal hybrids for chromosomes 1, 2, 5, 6, 7, 9, 13, 15, 17, and 21. (RPIS 10088)

State University of New York Health Science Center at Syracuse

Syracuse, NY 13210

Departments of Medicine and Microbiology

385. Construction of a Human Genome Library Composed of Multimegabase Acentric Chromosome Fragments

M.J. Lane

P. Hahn

J. Hozier

(315) 464-5446

\$338,000

This project is creating a human genome library composed of 5-Mb elements carried in mouse EMT-6 cells. In addition, new methods to detect overlaps between the elements are being

developed. This project involves infection or transfection of a human cell line with a selectable marker, selection of infected human cells, and lethal irradiation of a polyclonal population of the cells. Irradiation is being followed by polyethylene glycol-mediated fusion to a recipient mouse cell line with the capacity to rescue introduced DNA as circular double-minute chromosomes.

This type of library will significantly reduce (1) the time necessary to isolate genes that have been genetically mapped to less than 5 cM apart and (2) the number of independent elements required to construct a physical map of the human genome. (RPIS 10447)

University of North Carolina

Chapel Hill, NC 27599

Department of Biochemistry and Biophysics
Lineberger Cancer Research Center

386. Development of Human Viral-Based Genomic Library of 150 to 200 Kb Inserts

J.M.H. Vos

T.Q. Sun

R. Misra

(919) 966-6887

\$96,000

Libraries of human genomic DNA of 150–200 kb size would be a very useful resource in global mapping efforts. This project's objective is to develop and demonstrate methods for rapidly cloning and propagating the DNA spanning 150–200 kb average size exclusively in human cells, and to use these methods for gene isolation, gene mapping and mutation detection. The proposed cloning strategy is based on the development of viral-mediated gene transfer technology. The specific objectives are to generate a human genomic library which (1) covers the range of insert sizes suitable for mapping by sequence-tagged sites (STSs), i.e., 100 kb DNA fragments, (2) is stably maintained in human cells for the preservation of the human genomic ordering and imprinting, and (3) is viral-based for easy production and efficient shuttling between human cell lines. Such a library will be a valuable collection of reagents in support of plans to map, isolate, sequence, and assay genes and other functional genomic elements cloned on a mini-Epstein-Barr virus (EBV) plasmid in human lymphoblastoid cells. It will also produce EBV-based viral stocks of the library by lytic EBV induction. To establish such a viral-based human genomic library, this research aims to (1) establish an episomal human genome library of 150–200 kb inserts with an average size of 150–200 kb on a mini-EBV vector in human helper lymphoblastoid cell line, (2) produce a human genomic library of inserts with an average size of 150–200 kb packed as infectious EBV virions, and (3) prepare EBV-based infectious stocks of chromosome-specific human genomic libraries of inserts with an average size of 150–200 kb. (RPIS 10441)

Northeastern University

Boston, MA 02115

Barnett Institute

387. The Separation of DNA by Pulsed Field Capillary Electrophoresis

B.L. Karger

(617) 437-2867

\$223,000

The objective of this research is to develop optimized capillary gel electrophoretic procedures for the length-dependent separation of double stranded DNA fragments. This optimization of high resolution and speed is being accomplished through the use of pulsed field electrophoresis. The goal is to combine the power of capillary electrophoresis and the resolution of pulsed fields into a new approach to DNA fragment separation. Ultraviolet, fluorescence, and radioactive detection are being utilized, the latter for attomole analysis of fragments and hybridized species. These approaches contribute to the human genome effort by providing new and powerful methodologies for restriction mapping of wide size range of DNA.

The research plan has two parts: separation of 1–50 kb fragments and the separation of 50–500 kb fragments. For the smaller fragments, polyacrylamide gel columns are used with pulsed field electrophoresis. Collection of specific fragments is accomplished by electric field programming. For the larger fragments, injection is from agarose plugs. Both agarose and agarose/polyacrylamide columns are developed for these fragments. Validation of the methodology is being accomplished using well-defined portions of the *E. coli* genome. (RPIS 10256)

University of Pennsylvania

Philadelphia, PA 19104

Department of Human Genetics

388. Foundation for a Syntactic Pattern Recognition System for Genomic DNA Sequences

D.B. Searls

(215) 573-3107

\$213,000

DNA is a language; therefore, it should be possible to analyze DNA using the tools and techniques of computational linguistics, which offer both an intensively studied declarative representation (formal grammars) and an equally well-developed procedural interpretation (parsing). Many search algorithms now used for DNA are based on regular expressions; in the Chomsky hierarchy of languages, the corresponding regular languages (RLs) are at the lowest level of expressive power. Yet, biologically important features such as inverted repeats are context-free (CF) languages and not RLs. In fact, secondary structure in its full generality is nonlinear, nondeterministic, and inherently ambiguous—all formally defined language-theoretic properties with significant consequences for any generalized algorithmic approach to

pattern recognition. Other features of the language of DNA suggest that even CF grammars may not suffice—tandem repeats formally belong to the non-CF copy languages, and nonorthodox secondary structures such as pseudoknots are also not CF. The secondary and tertiary structure of proteins and the resulting interactions between residues suggest that genes themselves are also CF or greater, as does the nondeterminism of gene expression.

Genomic rearrangements may have marked effects on the nature of any underlying language. The CF languages, for example, are not closed under duplication, inversion, or transposition; i.e., when such evolutionary operations are applied to strings contained in a CF language, there is no guarantee that the resulting language will still be CF. Thus, evolution by its nature may provide pressure toward increasing linguistic complexity. Another such pressure may arise from superimposition of multiple levels of information, e.g., signals for successive steps in gene expression, because CF languages are also not closed under intersection.

A class of languages lying between CF and context-sensitive, called indexed languages (ILs), appears to be adequate for all the biological phenomena examined thus far. Using Prolog-based logic grammars, the researchers have implemented a formalism for string variables that appears to specify the required elements of ILs and have incorporated a number of other domain-specific features to allow for powerful pattern-matching search. The resulting system has been applied to "discovering" globin and tRNA (ribonucleic acid) genes in genomic sequence data. (RPIS 5647)

Promega Corporation

Madison, WI 53711

389. Site-Specific Endonucleases for Human Genome Mapping

R. Lowery

(608) 274-4330

\$500,000 (2-year funding)

Current large scale genome mapping methodology suffers from a lack of tools for generating specific DNA fragments in the megabase size range. To address this need, it is planned to develop a set of site-specific endonucleases capable of generating DNA fragments in the 2–100 megabase size range in a single step. Phase I demonstrated that the mobile group I intron-encoded endonuclease, I-Ppo, has excellent potential for use in general molecular biological and human genome research. This is because of its ability to be expressed and purified at high yields, its stability and activity under various reaction conditions, and its ability to efficiently cleave genomic DNA imbedded in agarose at a single site. To broaden the potential and develop the I-Ppo enzyme for human genome mapping and analysis of other complex genomes such as *C. elegans*, Phase II is designed to identify conditions and modifications that enhance I-Ppo's rare-cutting capabilities, isolate I-Ppo proteins with mutations that enable the nuclease to cleave at altered recognition sequences, test combinations of

conditions and modified forms of I-Ppo to extend the enzyme's cutting capabilities, and assess I-Ppo's ability to cut complex genomic DNA in agarose. Thus, Phase II provides a set of conditions and modified I-Ppo enzymes with a range of useful cutting frequencies for complex genomic mapping applications and a systematic structure-function analysis of a potentially novel type of DNA-protein interaction. These results should provide an excellent basis for commercialization efforts, which will focus both on immediate complex genomic research applications and on ultimate incorporation of I-Ppo into instrumentation used in genetic mapping.

Phase II should provide specific forms of native, mutated, and chemically modified forms of I-Ppo that cleave complex genomic DNA at specific recognition sequences in a single-step procedure. These enzymes will be commercialized in Phase III for both immediate genomic mapping research applications and incorporation into instrumentation for genomic mapping. In addition, Phase II provides data on (1) the structural interaction between the DNA binding site and I-Ppo, (2) reaction conditions caused by external agents that extend the cutting capabilities of I-Ppo, and (3) other select group I mobile intron-encoded endonucleases that may have similar cutting capabilities. This information will be used to develop and commercialize enzymes with complementary cutting capabilities. (SBIR)

Ransom Hill Bioscience

Ramona, CA 92065

390. High Speed Electrophoresis in a Solid Substrate

M.T. MacDonnell

(619) 789-9483

\$44,921

A method for the high speed electrophoretic separation of nested sets of nucleic acid fragments in a solid (i.e., nongel) substrate is being developed. The technique employs thin cellulose membranes as the supports for the separation of sequencing fragments in an electric field. Nucleic acid (DNA, RNA) fragments are driven through pores in a cellulose matrix. The cellulose matrix pore diameters are on the order of the diameter of double-stranded DNA. This is being accomplished by causing the DNA fragments to migrate by reptating (threading "end-on") through the cellulose matrix pores. Fragments become oriented end-on before they enter the cellulose matrix by way of short, steep pore gradient contiguous with the top of the cellulose membrane. A similar approach, using pore-limiting concentrations of polyacrylamide electrophoresis, has been shown to result in the high resolution separation of DNA restriction fragments in less than 1 minute. It is anticipated that this level of performance can be duplicated by employing similar pore diameters in a cellulose matrix. Additional advantages that could be afforded by the use of cellulose membranes for electrophoretic separations include their commercial availability and potential for long-term storage; unlike the neurotoxic acrylamide monomer and crosslinker, cellulose is nontoxic. In Phase I, rapid, reptative electrophoretic separation

of sequencing-sized fragments (i.e., in the range of 10–300 base-pairs) are being optimized by using thin cellulose membranes. Studies are being undertaken to determine the optimum (1) method for sample loading; (2) buffer conditions; (3) electric field parameters, including testing of contour-clamped homogeneous field conditions; and (4) storage conditions, shelf life, and reusability of cellulosic membranes.

The potential commercial application of the new technology derives from two sources: (1) the marked increase in throughput afforded by the employment of reptation (end-on migration) for the separation of sequencing fragments (results from pilot pore-limiting studies suggest that as much as a ten-fold increase in throughput can be expected from this approach); and (2) whereas polyacrylamide gels for sequence analysis are typically prepared in the laboratory by the end-user from reagents that are notoriously neurotoxic, cellulose membranes are readily available, easily stored, and will likely be reusable. These improvements translate directly into commercial advantages over conventional methods. (SBIR)

Rhode Island Hospital and Brown University

Providence, RI 02903

391. An Improved Method for Producing Radiation Hybrids Applied to Human Chromosomes

C.L. Jackson

H.F.L. Mark

(401) 277-4370

\$135,000

Our long-term goal is to develop and utilize radiation-hybrid cell lines containing overlapping regions of human chromosome 19 marked with a retroviral vector. The vector contains features designed to facilitate gene mapping, such as a new dominant selection system, sites for rare-cutter restriction enzymes, and a tRNA suppressor gene that allows easy cloning of the insertion site. A monochromosomal microcell hybrid containing a marked human chromosome 19 was isolated first. The retroviral vector insertion site in human chromosome 19 is cloned and localized to the 19p13-q12 region.

Radiation hybrids are produced at doses of 1,000 to 8,000 rads. Because of the selectable marker, these hybrids should have a stable fragment of chromosome 19 containing the chromosome region surrounding the inserted marker. These hybrids are fully characterized by several methods, including in situ hybridization, polymerase chain reaction, and Southern analysis. Additional retroviral vectors are used to obtain several hybrids containing chromosome 19 marked in different regions. The location of each marker is identified; regions of interest are isolated from rodent-human hybrids by irradiation and fusion. An overlapping set of radiation hybrids, with each hybrid containing only a small fragment of the original chromosome 19, is produced and its chromosome 19 regions are characterized and analyzed for markers. These hybrids aid in physically mapping chromosome 19 and in isolating specific sequences. (RPIS 10444)

Salk Institute for Biological Studies

La Jolla, CA 92037

Gene Expression Laboratory

392. Isolation of Specific Human Telomeric Clones by Homologous Recombination and Yeast Artificial Chromosome Rescue

G. Wahl

(619) 453-4100

\$151,000

This research pursues a new strategy for directly isolating telomeric and subtelomeric regions from human and other mammalian chromosomes. The strategy utilizes homologous recombination to target a vector to telomere proximal regions. The vector is designed to enable the rescue of the regions flanking both sides of the insertion site directly as yeast artificial chromosome (YAC) clones. The vector is endowed with selectable markers to enable amplification of the region flanking the insertion site and specialized restriction sites, which cut infrequently in the mammalian genome. Both of these features should facilitate the rescue of YACs up to and possibly exceeding 1 megabase and aid in developing long-range restriction maps of the targeted regions. The initial targets are the telomeric regions from chromosomes 19, 16, 5, and 2. Additional telomeric regions will be isolated as the cosmids or other clones derived from telomere proximal regions become available to provide the sequences required to prepare the targeting substrates. It is anticipated that the development of the telomere rescue strategy will greatly facilitate the goal of obtaining a complete map of the human and other genomes. (RPIS 10448)

Molecular Genetics Laboratory

393. Technology Development for Physical Mapping of Human Chromosomes

G.A. Evans

(619) 453-4100

\$390,000

The overall goal of this project is to develop new technologies for the construction of (1) large scale physical maps of human chromosomes and (2) complete clone sets using a minimum amount of effort and manpower. The strategy for mapping includes the high resolution localization of chromosome-specific landmark cosmids by in situ hybridization, followed by the isolation of yeast artificial chromosome (YAC) clones spanning the landmarks. Current techniques involving the individual analysis of each landmark clone and associated YAC are being improved by developing automated methods for the analysis and "multiplex" methods for YAC clone screening and mapping. Current research towards specific technological goals includes: (1) developing automated applications for chromosome mapping involving and including high density arrays of YAC clones on nylon or nitrocellulose filters, (2) developing and improving techniques for PCR and hybridization-based screening of YAC libraries for the isolation of individual clones, (3) developing techniques for detecting overlapping regions in YAC libraries by hybridization-based approaches

which will then allow rapid, simultaneous screening for multiple YAC clones in a multiplex approach, (4) developing technology for the rapid construction of contigs greater than 2 mb from combined YAC and cosmid clones, (5) developing methodology to detect genes (expressed sequences in cDNA libraries) within physical maps and isolating corresponding cDNA clones, (6) developing and improving techniques for determining the DNA sequences of cDNA clones isolated based on map position, and (7) converting existing genome databases derived in this lab to a multiuser networked environment compatible with computer systems at use in DOE National Labs. (RPIS 9865)

Stanford University
Stanford, CA 94305

Department of Human Genetics

394. Human Genetic Diversity

L.C. Cavalli-Sforza
(415) 723-5052

\$25,000

Cofunding through the National Science Foundation provides support for the organization of two workshops and an international conference on the development of a Human Genetic Diversity project. Human genetic diversity holds the key to understanding the evolution of our species. By documenting genetic variation, it will be possible to decipher the forces that guided our evolution and the paths down which it proceeded. The data are significant for both biological scientists and medical researchers. With the advent of new techniques for manipulating nucleic acids, there has never been a better time for gathering this data. However, the disappearance of many aboriginal populations places a time constraint on the gathering of the information. These sessions bring together mathematical population geneticists, statisticians, population biologists, and physical anthropologists to develop appropriate strategies for data gathering, storage techniques, and standardization of protocols, and to consider which populations need to be sampled. (RPIS 10711)

University of Texas
Houston, TX 77030

M.D. Anderson Cancer Center
Department of Molecular Genetics

395. Sequence-Tagged Sites for Human Chromosome 19 cDNAs

M.J. Siciliano
(713) 792-2910

\$207,000

This project implements a procedure for cloning human chromosome-specific expressed gene sequences in order to develop 900 sequence tagged sites (STSs) for expressed genes located on human chromosome 19. In the long term, the success of the

strategies and technologies employed here should be applicable to other chromosomes. From a human x Chinese hamster, interspecific somatic cell hybrid monochromosomal for human chromosome 19, an hn-cDNA library is made from heterogeneous (unspliced) nuclear ribonucleic acid (hnRNA) transcripts. The primers for this cDNA synthesis recognize 5' splice junction sites and therefore enrich for the isolation of expressed exons. Hn-cDNA library clones containing human inserts are isolated from the library and verified as to human chromosome 19 origin and regional assignment on Southern blots containing appropriate somatic cell hybrids. Up to 300 to 400 bp of the human inserts are being sequenced at the Lawrence Livermore National Laboratories (LLNL). Sequence analysis programs are used for each insert to (1) determine whether a similar fragment has been previously sequenced, (2) estimate the probable exon segment of the unique sequence region, and (3) evaluate the presence in the fragment of Alu-linked poly-A tandem repeats associated with high levels of polymorphism. Polymerase chain reaction (PCR) primers are made for the probable exon segment of the unique sequence region of each fragment, making the segment an STS. Primers are being used to verify the map position of the STSs onto human chromosome 19 by concordant segregation analysis on hybrid clone panels by PCR. Primers are also being made available to LLNL for assignment of the STSs to the physical chromosome map being developed there. The same PCR primers are used to determine the expression of STSs in RNA messages from a series of tissue types. (RPIS 10574)

Tropix, Inc.
Bedford, MA 01730

396. Development of Chemiluminescence-Based DNA Sequencing Kits and Systems

I. Bronstein
(617) 271-0045

\$500,000 (2-year funding)

The Phase II objective is to develop a set of test kits for DNA sequencing using chemiluminescent detection. Information acquired during Phase I demonstrated the feasibility of using the chemiluminescent signal detection from an alkaline phosphatase substrate disodium 3-(4-methoxyspiro[1,2-dioxetane -3,2'-tricyclo[3.3.1.1^{3,7}]decan]-4-yl)phenyl phosphate, known as AMPPD to visualize polynucleotides in blots. Two types of sequencing kits, both based on the Sanger dideoxy technique, are being developed. One of these kits has biotinylated primers based on M13 vector; the second has biotinylated dideoxynucleotide triphosphate terminators. The kits contain various components including polymerase, nylon membrane, buffers, avidinalkaline phosphatase conjugate, AMPPD, and other reagents, as well as detailed experimental protocols to facilitate obtaining reproducible chemiluminescent-based sequence data. In addition, a charge-coupled device-based (CCD) image camera system is being evaluated. This system enables data to be directly acquired and processed from the chemiluminescent sequencing blots. Advantages of this system include sensitive, rapid, nonisotopic detection; excellent DNA band resolution; stable, inexpensive

reagents; and automated signal acquisition. In addition, kits are provided to allow users to assay reagents for alkaline phosphatase contamination which would severely interfere with the chemiluminescent assay.

Anticipated benefits of this program include development of nonisotopic sequencing components and kits for commercial use. Kits and systems will improve the efficiency of DNA sequencing because the chemiluminescent signal can be detected within minutes of exposure. A CCD-based camera system will further improve the efficiency of data acquisition. (SBIR)

397. Chemiluminescent Multiprimed DNA Sequencing

C.S. Martin

(617) 271-0045

\$50,000

The objective of this study is to improve the efficiency of performance of a nonisotopic detection method for DNA sequencing. A chemiluminescent detection procedure using 1,2-dioxetane substrates for alkaline phosphatase has been developed. With this method, DNA sequencing reaction products labeled with biotinylated primers are imaged following electrophoresis by transfer of the separated DNA fragments to nylon membrane, with 1,2-dioxetane substrates. Upon dephosphorylation, these enzymatic substrates decompose and emit light. In Phase I, the feasibility of increasing the amount of DNA sequence information that can be imaged from one membrane is assessed by separating multiple sets of DNA sequencing reactions in each lane of the gel, transferring the DNA to nylon membrane, and detecting each set of sequencing reactions individually. This is accomplished by utilizing multiple DNA sequencing primers for the DNA sequencing reactions. The primer for each reaction contains its own unique label. Each set of DNA sequencing reactions is detected with an alkaline phosphatase conjugate specific for the label. The performance of various labels and enzyme conjugates is evaluated. The goal of the study is the development of optimum procedures for rapid detection of each set of labeled DNA fragments. If the research is successful, newly developed protocols and the individual reagents will be incorporated into a research kit that will become a useful tool for molecular biologists for DNA sequencing.

DNA sequencing kits will be developed for use with several labeled primers that will permit sequential imaging of multiple sets of DNA sequencing reactions with chemiluminescence from 1,2-dioxetane substrates. (SBIR)

University of Utah

Salt Lake City, UT 84112

Department of Chemistry

398. Field-Flow Fractionation of Chromosomes

J.C. Giddings

(801) 581-6683

\$128,000

Field-flow fractionation (FFF), a powerful and versatile methodology of relatively recent origin, is applicable to the separation of virtually all categories of macromolecules and particles. The object of this study is to apply state-of-the-art FFF methods to chromosomes, in an effort to separate and purify them from one another and from background cellular debris. This research is focused primarily on the utilization of sedimentation/steric FFF for this problem, but other FFF techniques, including flow FFF, may be involved as well. Recent experiments involve particles in the chromosome-size range. In all likelihood, FFF methods have sufficient flexibility to circumvent any potential problems encountered in chromosome separation, such as chromosome adsorption or disruption. (RPIS 10063)

Department of Human Genetics

399. Advanced Sequencing Technology

R.F. Gesteland

R. Weiss

(801) 581-5190

\$504,000

Further development of multiplex sequencing includes an automated sequence reading system for collection of data and a front end system for organizing the input clones to avoid shotgun approaches. The gel reading system is based on a new algorithm using communication and signal processing theory. The front end system employs transposons that carry in primer sequences necessary for multiplex sequencing. A rapid mapping method to identify the minimal set of DNA fragments is under development. These projects are being pursued in parallel with development of (1) capillary gel sequencing and (2) comprehensive computer systems for accumulating and analyzing DNA sequence information, which are parts of the program of the Utah Center for Human Genome Research. (RPIS 9857)

University of Washington

Seattle, WA 98195

Department of Molecular Biotechnology

400. Megabase Sequencing of Human Immune Receptor Loci

L.E. Hood

(206) 685-7367

\$470,000

The primary focus of this project is the complete sequencing of the three human T-cell receptor gene families, which comprise more than 3 Mb. Later stages of this research will initiate

studies on the human HLA locus, which also covers about 3 Mb. Three major goals for this project include (1) evaluating new strategies, techniques, and instrumentation for large-scale DNA sequence analysis, (2) determining the base sequence for human T-cell receptor and HLA loci, and (3) using this information to create new approaches to studying the molecular biology of the immune response. Efforts are based on using four-color, automated fluorescent DNA sequencers and a mixed shotgun/directed approach with Sanger sequencing methods. The enormous amount of sequence data generated in this project provides an invaluable tool for dissecting the fundamentals of the human immune system and for constructing a paradigm for understanding basic molecular biological systems. (RPIS 10744)

401. Vertically Integrated Analysis of Human DNA

M.V. Olson

(206) 685-7367

\$300,000

A systematic approach is being developed to the vertically integrated analysis of segments of human DNA ranging up to a few megabase pairs in size. Vertical integration denotes sequential analysis of a genomic region at all levels of detail from low resolution physical mapping to finished sequence. The emphasis in this project is on the steps upstream from DNA sequencing, particularly the hierarchical analysis of genome segments in somatic cell lines, yeast artificial chromosomes, cosmids, lambdas, plasmids, and filamentous-phage clones. The end result is precise, high resolution physical maps on which the ends of the inserts of small insert clones, suitable for use as sequencing templates, are placed exactly.

The project emphasizes experimental strategies judged to be good candidates for high level automation. Only simple, modular experimental steps are employed. The raw data are captured by the electronic imaging of electrophoretic gels whose banding patterns have sufficiently predictable characteristics that completely automated interpretation is expected to be practical. Early steps are being explored on a path toward automation of these procedures on a scale that would allow the analysis of millions of clones. (RPIS 10745)

WGBH Educational Foundation

Boston, MA 01778

402. *The Secret of Life*

P. Apsell

G. Chedd

(617) 492-2777

\$50,000

The Secret of Life is a series of eight 1-hour television documentaries for the Public Broadcasting System (PBS), to be broadcast in late 1993.

The goal of the series is to make the new biology intelligible to audiences, demonstrate the extent to which it has transformed the biological and medical sciences, and explore the pressing issues it raises. *The Secret of Life* helps to close the information gap that currently exists between molecular biologists and the general

public by preparing viewers to act as informed citizens in debates that demand the widest possible participation. In addition to the PBS series, the project is producing a companion trade book, a college telecourse, high school video segments, and an interactive videodisc.

The Secret of Life is being produced by WGBH in conjunction with the British Broadcasting Corporation and the Chedd-Angier Production Company. (RPIS 10672)

University of Wisconsin

Madison, WI 53706

Department of Chemistry

403. Automation of the Front End of DNA Sequencing

D. Mead

L.M. Smith

(608) 263-2594

\$249,000

This research is developing an automated front end system for large scale DNA sequence analysis. The system performs purification, mapping, fragmentation, fractionation, cloning, and enzymatic extension steps. When fully implemented, it will be capable of producing extension reactions from 1,000 DNA templates per day, a rate that translates into approximately 500,000 bases of raw sequence data per day. To achieve this goal, the plan outlines development of technologies for (1) solid-phase purification of bacteriophage lambda or cosmid DNA, as well as the recombinant inserts, (2) simple and efficient DNA fragmentation and fractionation, (3) automatic cloning and mapping vectors, (4) micro-sequencing instrumentation, and (5) a directed end-sequencing strategy. The methodology includes an automated flexible robotic liquid dispensing instrument capable of controlling multiple parameters and large numbers of samples. (RPIS 10431)

404. High Speed DNA Sequence Analysis by Matrix-Assisted Laser Desorption Mass Spectrometry

L. Smith

B. Chait

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\$215,000

This project is developing an ultra-fast, accurate mass spectrometric method for sequencing DNA fragments. The method uses a given template to generate four sequencing reactions (by either the Sanger or Maxam-Gilbert procedure) followed by four consecutive, ultra-rapid mass spectrometric measurements of the resulting mixtures. The mixtures are not separated into individual components prior to measurement. The mass spectral data is analyzed by the same methods as those employed for ladders separated on electrophoretic gels.

This research applies the revolutionary new technique of matrix-assisted ultraviolet (uv) laser-desorption mass spectrometry to the measurement of nucleic acid mixtures. Specifically, it plans to (1) develop and improve the matrix-assisted uv

laser-desorption technique for measuring DNA ladders to obtain a resolved mass spectrum of a mixture containing 100–200 products of a given sequencing reaction (DNA fragments up to 500 bases long), (2) determine the base sequence of the DNA fragment by automatically comparing the mass spectra from four sequencing reaction mixtures in a manner exactly analogous to that used with electrophoretic gels, and (3) improve the accuracy of the present sequencing procedure over gel-based procedures by requiring that the absolute masses of two adjacent sequencing reaction products differ by the mass of a single base. (RPIS 10437)

405. High Speed Automated DNA Sequencer

L.M. Smith

(608) 263-2594

\$279,000

This continuing project has five specific aims: (1) Design and build a second generation fluorescence-based ultra-thin gel DNA sequencer with a larger (2.5 cm x 2.5 cm) charge coupled device detector utilizing from-the-side laser excitation. System capacity is 450 bases of raw sequence data per hour from each of 48 samples, or 21,600 bases per hour. (2) Design and build an automated loading system capable of loading the 48 samples onto the gel for analysis. (3) Develop software for sequence determination from the data produced in the fluorescence instrument. Integrate the software into a system capable of assembling the large amounts of data produced by the system. (4) Investigate several approaches to increasing the performance of the gel systems, including alternative denaturants to urea for sequencing gels, alkaline gels, discontinuous "stacking" buffer systems, and pulsed-field methods. (5) Put the instrument to use in limited scale (10-20 kb) sequencing projects to assist in its tuning/optimization. (RPIS 10297)

Department of Computer Science

406. Applying Machine Learning Techniques to DNA Sequencing Analysis

J.W. Shavlik

M.O. Noordewier

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\$218,000

The Human Genome Project will produce large amounts of uncharacterized DNA sequences. Due to the magnitude of this data, automated analysis techniques must be developed. These algorithms should recognize important intragenic regions of the DNA sequences and categorize them, thereby allowing biological and medical researchers to focus their attention on promising and manageable subsets of the data. The ability to analyze individual genes and the proteins they encode has in the past greatly increased the understanding of genetic disorders, the immune system, infectious diseases, and cancer. Automating aspects of sequence analysis promises to support further advances.

This research applies and extends a machine learning algorithm that modifies existing knowledge about biological sequences. It does this by considering sample members and nonmembers of the sequence motif being learned. Using this information, the learning algorithm produces a more accurate representation of the knowledge needed to categorize future

sequences. Specifically, the algorithm maps inference rules, such as consensus sequences, into a neural (connectionist) network. Neural network training techniques then use the training examples to refine these inference rules. Neural networks represent knowledge in an opaque form; this project converts the results of the neural learning algorithm into a human-interpretable form.

Preliminary investigation, in which the system learned how to recognize promoter regions in *E. coli* DNA sequences, indicates the approach is more powerful than standard techniques in the biological literature, as well as alternative machine learning algorithms. This project is evaluating further the applicability of the Knowledge-Based Artificial Neural Network (KBANN) approach to molecular biology, systematically comparing it to alternate techniques, and investigating its dependence on the amount of training data and sensitivity to sequence errors. Systems are being trained to recognize additional features of DNA sequences, including complete prokaryotic and eukaryotic genes. These recognizers are being distributed for use by molecular biologists, who need not know about neural networks to make use of the recognizers.

The project is also extending the existing KBANN algorithm in biology-specific ways. The field of machine learning is at a level of maturity where further progress can best occur by applying existing techniques to important "real-world" tasks. This research promises to develop useful automated devices for recognizing several important entities in DNA sequences, produce useful tools for easing the development of such devices for additional sequence features, and advance the state of the art in machine learning. (RPIS 10436)

WNET/THIRTEEN

New York, NY 10019

407. Medicine at the Crossroads

G. Page

S. Moore

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\$50,000

Thirteen/WNET in New York, the major producer of scientific documentaries for PBS and its more than 300 member stations, is planning an important new public television series called *Medicine at the Crossroads*, which is highly relevant to DOE's Human Genome Program. Planned as the PBS prime time centerpiece for spring 1992-1993, the eight-part series will explore the tensions between advances in bioscience and technology and the needs of society. Its objective is to illuminate the meaning of medicine in people's lives—scientifically, socially, and philosophically. Because human genome research profoundly affects the practice of medicine, the scientific basis of the Human Genome Initiative and its ethical and legal implications must be made accessible to the American public. Keys to the success of the Human Genome Initiative are creating awareness and public support of the mapping and sequencing of the human genome and fostering an understanding of how this knowledge and its application will help society cope with illness related to environmental risk and workplace safety. *Medicine at the Crossroads* can play an integral role in this public information and education process. (RPIS 10575)

Biotechnology: Structural Biology

Intramural DOE Laboratories

Argonne National Laboratory

Argonne, IL 60439

Biological and Biomedical Research Division

408. Protein Structure and Conformation

M. Schiffer

(708) 252-3883

\$745,000

This program determines fundamental structural and conformational relationships for key biological molecules, including immunoglobulin light chains, antibodies, and the photosynthetic reaction center. It uses biophysical techniques, principally x-ray diffraction for crystalline material and gel filtration for molecules in solution. X-ray diffraction techniques are used to determine the detailed three-dimensional structure of human Bence Jones proteins, which serve as excellent models for intact antibody molecules and provide significant information about the antibody binding site. These proteins and other representatives of the immunoglobulin superfamily also provide information on the relative positions of the immunoglobulin domains and the molecular basis of interdomain interactions. New methods are studied for efficient quantitative evaluation of antibody binding properties. The models used are antibody molecules with binding characteristics against various antigens, including some that bind other antibodies. Anti-idiotypic antibodies and auto-antibodies such as rheumatoid factors represent important elements of normal and abnormal immune responses, studies of which increase knowledge of immune regulation. Other model studies focus on hybridoma-produced monoclonal antibodies, reagents of increasing biotechnological importance. The photosynthetic reaction center, which carries out the first step of photosynthesis, is also investigated. This is one of the first integral membrane proteins for which a structure has been determined at atomic resolution and which retains biological activity in its crystal form. (RPIS 0106)

409. Charged Coupled Device Area Detectors for Synchrotron X Rays

E.M. Westbrook

(708) 252-3983

\$405,000

A marriage of synchrotron x-ray sources with electronic area detectors creates the best possible tool for structural biology research. A synchrotron x-ray beamline can direct huge fluxes of x rays onto small protein crystals, permitting data to be recorded in short time increments or from small crystals. Because many proteins do not form large crystals, synchrotron radiation can expand the scope of research into protein structure and function. Further, many biological processes

occur quickly, so the ability to record diffraction data rapidly permits examination of processes in motion on time scales that are biologically meaningful. However, accurate data collection requires accurate recording methods. Photographic film is currently the only recording medium that can accept the high x-ray flux of synchrotron. Film is inaccurate and inconvenient, cannot be easily automated, and cannot be used to input data directly into computers. Electronic area detectors based upon the charged coupled device (CCD) are the most promising medium for recording x-ray diffraction data at synchrotron. CCD detectors record two-dimensional diffraction patterns without limit in flux, with high spatial resolution, accuracy, and efficiency, and with fast time response. In addition, the images are transmitted directly to computers for storage and for instant review during data collection. CCD detectors are controlled to record data with time increments shorter than a millisecond, permitting many biological processes to be studied in motion. CCD detectors have been built for protein crystallography. More research steadily improves and develops their design and application. These detectors are valuable for any synchrotron x-ray source used for structural biology and are particularly useful for biological applications of Argonne National Laboratory's Advanced Photon Source. (RPIS 4919)

410. Biomedical Beamlines for APS Synchrotron

E.M. Westbrook

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\$915,000

A well-designed synchrotron x-ray beamline can direct huge fluxes of x rays onto small protein crystals, permitting data to be recorded in short time increments or from small crystals. Protein crystals diffract weakly because the crystals are small and their unit cells are large. The high x-ray flux available at synchrotron sources can improve the diffraction data quality of these crystals, while the wide energy range of x rays available from synchrotron sources permits the application of Laue diffraction methods and multiple-energy anomalous dispersion phase determination methods. Thus, development of new synchrotron beam lines for protein crystallography has a significant impact on research into protein structure and function. The Structural Biology Center (SBC) fosters development and operation of synchrotron beamlines for protein crystallography. The SBC is developing two beamlines for protein crystallography at the National Synchrotron Light Source: X8C and X26C. When these are fully operational they operate as user facilities. This project also involves designing, building, and operating a national user facility for structural biology at the Advanced Photon Source (APS), a new synchrotron source being built at Argonne National Laboratory. This new facility contains one sector of the APS (a sector consists of an insertion device x-ray source and its adjacent bending magnet x-ray source) which is optimally designed for diffraction studies in structural biology. Such applications are quite important, they have an effect on society and make contributions to basic science. The goal of SBC is to operate user-friendly, efficient applications of modern hardware and software to achieve rapid data acquisition and processing. (RPIS 5191)

Brookhaven National Laboratory Upton, NY 11973

Biology Department

411. Synchrotron X-Radiation Scattering Spectrometer for the Study of Biological Structures

M.S. Capel

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\$320,000

This facility is for time resolved x-ray diffraction at the National Synchrotron Light Source of Brookhaven National Laboratory. The time structure, large radiation flux, and wavelength tunability of this x-ray source provide unique possibilities for the study of oriented biological specimens (e.g., muscle or membranes) and biomolecules in solution. When fully operational, the small-angle scattering spectrometer will permit rapid, automated structural studies of very small and/or dilute sample volumes. The high data collection rates of locally designed and built position sensitive x-ray detectors enable novel time-dependent studies of biological processes. The attendant user-support program promotes the development of x-ray diffraction for biological structural analyses. (RPIS 4962)

412. Transcription in Eukaryotes

P.V.C. Hough

(516) 282-3384

\$150,000

This program characterizes protein-DNA structures that initiate eukaryotic transcription and DNA replication using scanning transmission electron microscopy.

The well-known transcriptional activator protein, Sp1, has been shown to function also as a transcriptional enhancer. The mechanism of enhancement involves Sp1 tetramerization, with the zinc-finger DNA binding domain of one constituent monomer binding to the remote enhancer site and that of a second monomer to a local Sp1 site; the intervening DNA is looped out. Multiple tetramers are also observed; such a higher order link structure significantly increases the concentration of activator protein at the promoter.

A candidate mammalian replication initiation protein named RIP60 is observed to bind to a defined sequence at the hamster dihydrofolate-reductase origin of bidirectional DNA replication, where it induces DNA looping and assembles high multimers involving the loop DNA.

Cloned yeast TFIID induces a hairpin structure specifically at the TATA element of the adenovirus major late promoter. However, cloned human TFIID induces hairpins in other regions as well. This difference suggests that the sample of human TFIID may have contained a contaminating protein with hairpin forming activity at additional recognition sequences, a possibility currently being investigated. (RPIS 4422)

413. Structural Studies on Proteins by X-Ray Diffraction

C.L. Lawson

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\$210,000

The three-dimensional structures of proteins and protein: ligand complexes are being investigated by x-ray crystallography. Emphasis is in two areas: (1) high resolution structural analysis, to learn how structural and chemical properties direct specific molecular interactions and (2) determination of new protein structures to investigate structure-function relationships. This approach provides a three-dimensional view of molecular interactions in biological processes.

The following projects are being pursued. First, the chemical and structural properties of a well-characterized, L-tryptophan binding protein are being investigated by determining structures of a series of related protein: tryptophan analogues. Second, crystallization of several proteins and protein:ligand complexes is being attempted to determine the structure and analysis of structure-function relationships. Priority is being given to proteins studied in the biology department. The projects use the crystallographic facilities at Brookhaven National Laboratory. (RPIS 0022)

414. Structural Studies on Chromatin and Ribosomes

V. Ramakrishnan

(516) 282-3388

\$250,000

This is a study of various aspects of chromatin higher order structure, using small angle neutron scattering and scanning transmission electron microscopy. Crystallographic studies are carried out on specific chromosomal and ribosomal proteins. The DNA of eukaryotes is present in the cell in the form of chromatin, whose basic structural unit is a nucleosome. The nucleosome is a complex of DNA with an octamer of histones. Histone H1, or its counterpart H5 in avian erythrocytes, plays a crucial role in the organization of nucleosomes into a higher order structure. This project focuses on the structure of H1/H5, its location in chromatin higher order structure, and details of its interaction with the nucleosome. Ribosomes are complexes of RNA and several proteins that play a central role in the translation of the genetic code to produce proteins. This project studies the location and structure of individual components of the ribosome. In addition, the project fosters collaboration with other scientists on the application of small angle scattering to study the conformation in solution of molecules of biological interest. (RPIS 0048)

415. Instrumentation Development for Neutron and Synchrotron Radiation Studies of Biological Systems

D.K. Schneider

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\$165,000

This project is developing adequate instrumentation for efficient use of new radiation sources like synchrotrons and high flux beam reactors in analyzing biological systems.

Developments in instrumentation during the last decade have improved the capabilities of neutron spectrometers, allowing experiments of greater sophistication to be performed. These developments include high resolution area detectors, thin-film multilayer monochromators, neutron guides, and fast data collection computer devices. These innovations have to be incorporated into spectrometers designed for a specific radiation source and for specific applications. Thus, the study of membranes containing sodium potassium ATPase or polymers such as DNA requires instrumentation with a unique combination of features including a high resolution area detector, adjustable wavelength with tunable bandwidth, and capability for time-resolved data collection. The recent availability of very intense synchrotron sources provides biophysicists interested in macromolecules with entirely new capabilities. These new tunable x-ray sources routinely provide anomalous diffraction to directly determine the phases of diffraction data. The very high flux from these sources allows observation of reaction intermediates in enzyme crystals, using Laue film diffraction techniques. Such techniques require a detector with an overall counting rate of 10^8 counts/sec. In addition, computer data handling techniques are needed to store and analyze these time resolved, two-dimensional data arrays. To use anomalous phasing techniques, monochromator systems with reproducible wavelength selection to within < 1 eV must be developed. (RPIS 4783)

416. Study of Biological Structures by Neutron Diffraction

B.P. Schoenborn
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\$905,000

Neutron diffraction techniques are being used to clarify the structure and function of proteins, protein complexes, and membranes. X-ray and neutron-scattering techniques are a major tool in the study of functional perturbations of protein and membrane activity by cofactors, substrates, drugs, and inert gases like anesthetics and industrial solvents.

Neutron scattering is an ideal technique for the analysis of biological structures because it permits the elucidation of structural details not attainable by other techniques. Neutron scattering is often preferable to x-ray scattering because the sample's constituents present a higher contrast to neutrons, thereby localizing the hydrogen atoms. Replacement of H_2O with D_2O changes the contrast and reveals the localization of hydrogen exchange regions, thus facilitating the identification of structural landmarks in chemical terms.

The neutron-scattering research program in the U.S. has been reviewed several times in the past few years. Although our scientific program is extremely strong, instrumentation in the U.S. lags behind that of Europe in several significant ways. A mini guide hall expansion plan provides the U.S. with state-of-the-art instrumentation and additional ports for neutron-scattering equipment. This expansion includes two versatile small angle stations for the study of biological complexes. (RPIS 0021)

417. Structural Biology Initiative

F.W. Studler
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\$1,000,000

Brookhaven National Laboratory (BNL) has a unique set of facilities for structural biology, including stations for x-ray scattering and ultraviolet spectroscopy at the National Synchrotron Light Source (NSLS), stations for neutron scattering at the High Flux Beam Reactor (HFBR), and the Scanning Transmission Electron Microscope (STEM) for high resolution measurement of molecular shapes and masses. These facilities provide a powerful combination of tools for examining the structures of individual macromolecules such as proteins and nucleic acids, and larger assemblies such as ribosomes, chromatin, viruses, and membranes. The already considerable demand for access to these facilities by researchers from universities and industry will intensify with the burgeoning demand for structural information in molecular genetics, biotechnology, genome research, and medicine.

This project is designed (1) to maximize the utilization and scientific impact of the current BNL facilities for structural biology, through an increase in basic scientific and technical support and through capital upgrades; (2) to enhance present capacities by providing a core facility for producing proteins for structural studies, adding an electron microscope for frozen hydrated specimens and a Scanning Tunneling/Atomic Force Microscope to the STEM facility, and constructing additional stations for x-ray and neutron crystallography at the NSLS and HFBR; and (3) to implement a training program to increase the pool of investigators equipped to use these sophisticated facilities for leading-edge research in structural biology. (RPIS 5486)

418. Ultraviolet Radiation Damage to DNA

J.C. Sutherland
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\$180,000

Ultraviolet (UV) and visible radiation from the sun and synthetic sources affect living organisms in ways that are both harmful and beneficial. Modern technologies may alter the intensity and spectral distribution of solar radiation reaching the Earth and thus change the existing balance between its harmful and beneficial effects. New synthetic light sources may also alter this balance. Realistic evaluation of the possible biological hazards of visible and UV-radiation requires an understanding of their various, sometimes antagonistic effects. This project studies the damage inflicted upon DNA irradiated both in vitro and in vivo and relates specific types of molecular damage to cell death, mutation, and cancer induction. It is particularly concerned with developing procedures for quantitating the damage done to the DNA of human skin irradiated in situ, and the subsequent repair of this damage. (RPIS 1823)

419. Synchrotron Ultraviolet User Facility*J.C. Sutherland**(516) 282-3406***\$190,000**

Ultraviolet radiation from the National Synchrotron Light Source is used to probe the structure and dynamics of biological molecules using circular dichroism (CD) and fluorescence spectroscopy. CD experiments on proteins, nucleic acids, and polysaccharides focus on wavelengths from 160–200 nm, a region of the spectrum where conventional light sources are less intense than the synchrotron. Fluorescence experiments use the broad spectrum, pulsing nature, and brightness of the synchrotron source to elucidate the structure, dynamics, and excited state reactions of nucleic acids, proteins, and their components.

This project supports the operation, maintenance, and continuing development of the CD and fluorescence experiments at port U9B, which are used by scientists from the Brookhaven National Laboratory, universities, and other research institutions. (RPIS 4831)

420. Protein Crystallography by Synchrotron Radiation*R.M. Sweet**(516) 282-3401***\$500,000**

X-radiation produced by the National Synchrotron Light Source (NSLS) at Brookhaven National Laboratory is a powerful tool for investigating biomolecular structure. Synchrotron radiation extends the use of x-ray diffraction methods by providing a much higher intensity beam, with adjustable wavelengths, than is available with conventional sources. The brighter beam allows data collection at higher speeds and with higher resolution.

An area diffractometer for crystallography, which provides immediate digitization of diffraction patterns, has been in use at beam line X12-C of NSLS. The tunable synchrotron beam allows measurement with this instrument of data for multiwavelength anomalous diffraction phasing. This program is developing methods and software to make the use of the instrument convenient and efficient.

The program encourages collaboration and service to outside users. Significant effort is put into training visitors in synchrotron science and the principles and practice of operation of the facility. The project supports crystallographic studies and collaborates in preparation of crystals for new structural investigations.

Significant progress has been made in the use of polychromatic Laue-diffraction methods for very rapid measurement of diffraction data. (RPIS 3625)

421. Scanning Transmission Electron Microscope Operation and Development*J.S. Wall**(516) 282-2912***\$105,000**

The Brookhaven Scanning Transmission Electron Microscope (STEM) Facility is recognized as a leader in state-of-the-art biological electron microscopy. To maintain this position, the

instrumentation must be upgraded constantly. It is most desirable to carry out these improvements without compromising the high productivity of the outside user program.

This project continues development of a new STEM employing electron energy loss spectroscopy (EELS) for chemical analysis of biological samples. Previous EELS studies have been limited by radiation damage and have yielded little of the information potentially available. Two new developments promise to overcome these limitations: (1) parallel readout detectors and (2) alignment and averaging of low dose images to simulate high dose conditions without damage. This technique is complementary to the present specific labeling schemes and should permit a wide variety of studies, such as determination of sites of phosphorylation on proteins and localization of RNA in relation to the proteins in ribosomes.

A second initiative in high coherence phase contrast microscopy has begun with the acquisition of a CryoEM from Duke University. This instrument has a superconducting objective lens and field emission electron gun, giving it the potential to be the best available instrument for studies of frozen hydrated specimens; however, it needs significant upgrades to become part of the user facility. (RPIS 0225)

422. Studies of Biological Structures by Scanning Transmission Electron Microscope*J.S. Wall**(516) 282-2912***\$220,000**

The electron microscope is a major tool for the study of the structure of living matter. Major improvements in this instrument can provide new insights into the health effects associated with various energy technologies. A Scanning Transmission Electron Microscope (STEM) was constructed at Brookhaven National Laboratory (BNL) for biological structure determination at 2.5 Å resolution on frozen specimens.

The BNL STEM is the only instrument of its type in the U.S. equipped for low temperature studies. It offers many capabilities surpassing those of conventional electron microscopes. The method of image formation is similar to that of a television set, one point at a time. The high information collecting efficiency of the STEM allows imaging of biological molecules with an order-of-magnitude lower radiation damage than in other electron microscopes. The STEM can easily image unstained biological molecules and single atoms heavier than bromine.

The ability to produce simultaneous images of the biological matrix of carbon atoms and the positions of specifically attached heavy atoms will give new insight into the structures and interacting systems of molecules. Specific heavy atom stains can be used to localize with near atomic resolution sites of interest. The quantitative nature of STEM imaging permits direct measurement of the molecular weight of single molecules or macromolecular complexes, thus establishing a direct link to biochemistry. The STEM is operated as a users' facility open to outside scientists through the assistance of a National Institutes of Health Grant. (RPIS 4427)

Instrumentation Division

423. Biophysical Instrumentation Research

V. Radeka

G. Smith

(516) 282-4266

\$350,000

This project is researching and developing instrumentation methods and techniques for biological research that uses synchrotron radiation and neutrons. The development of several classes of position-sensitive detectors is essential for x-ray and neutron scattering studies of biological molecular structure. Researchers are emphasizing precision and extremely high counting rates for synchrotron radiation as well as high precision for thermal neutrons.

Experimental and theoretical studies are conducted on fundamental problems in photon and particle detection, such as the physics of detection processes, properties of detection media (gas, liquid, and solid), signal formation, noise, and position-sensing methods. Use of detectors at the National Synchrotron Light Source and the High Flux Beam Reactor provides operational tests, while continuing user feedback provides guidance for future initiatives.

Position-sensitive detectors with significantly improved capabilities have been produced. A class of x-ray and thermal neutron imaging detectors with the highest known accuracy and long-term stability has been developed. X-ray detectors with the highest known count rate capability, the best position linearity, and radiation hardness have been produced.

The work of these researchers should continually improve understanding of the fundamental processes of radiation detection. X-ray and neutron detector performance should be further improved, leading to new instrumentation for the rapidly evolving techniques employed in synchrotron radiation research.

This work should provide basic tools for x-ray and neutron scattering studies of biological molecular structures. Other areas that need accurate detectors (e.g., materials science, chemistry) should also benefit. (RPIS 3626)

Lawrence Berkeley Laboratory

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Cellular and Molecular Biology Division

424. Application of X-Ray Microscopy To Study Protein Secretion

S.S. Rothman

(510) 486-4029

\$350,000

This biological research program seeks (1) to establish common ground to study substantive biological problems with emerging x-ray microscope techniques and (2) to develop the necessary tools to do so effectively. The problems to be addressed in the program will technically advance the method for biological research and yet have features amenable to study with a developing methodology. Work is being done with the

National Synchrotron Light Source (NSLS), while at the same time aiming at more advanced capabilities at the Advanced Light Source in Berkeley. Initial experiments center on an important proof of principle for the method: imaging biological samples in the native state (in physiological environments) at high resolution. Using the elemental information provided by the method, the project has obtained quantitative values for the protein content of single cellular organelles. This success opens the door to many opportunities to study the relationship between native state structure and function at the subcellular level with spatial resolution almost an order of magnitude beyond that of the optical microscope. (RPIS 5471)

Chemical Biodynamics Division

425. Self-Processing Ribonucleic Acid

J. Hearst

I. Tinoco

D. Wemmer

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\$380,000

This research is identifying the properties of a self-processing ribonucleic acid (RNA) molecule. The RNA itself is a 359-base-long satellite RNA of tobacco ringspot virus that is an infectious agent of plants. The mechanism of autocatalysis is inherently different from that of any other self-processing RNA described because the molecule is able to cleave and relegate one of its own phosphodiester bonds through a mechanism that appears similar to normal acid/base catalyzed hydrolysis, but cleavage is at a single unique site in its sequence.

Project tasks designed to increase understanding of this phenomenon are (1) determination of the minimum size necessary for this molecule to carry out the self-processing reaction, (2) production of large quantities of the minimum processing size RNA, (3) probing of the RNA with structural specific nucleases to identify structural regions, and (4) reaction of the RNA with psoralen, which crosslinks at certain bases that are both sequence and structure specific, to identify structural regions. In addition, the project is investigating: (1) nucleotide substitutions that give altered base sequences to define both base specific and structural requirements of the processing reaction, (2) growth of crystals for x-ray diffraction, and (3) phylogenetic comparisons of related satellite RNAs, all of which are self-processing, thereby allowing structural predictions to be made based on conserved regions.

The project is attempting to produce large quantities of slowly cleaving analogues, develop methods for incorporation of isotopic labels, and carry out nuclear magnetic resonance analysis of secondary and tertiary structure elements to determine their relationship to activity. (RI IS 5030)

426. Structural Biophysics*S.-H. Kim**(510) 486-4333***\$335,000**

Whereas all cellular ras oncogenes have a single activating mutation, retroviral ras oncogenes isolated from Harvey (v-H-ras) and Kirsten (v-K-ras) murine sarcoma viruses have double mutations involving residues 12 and 59. The glycine residue is mutated to either an arginine in v-H-ras or to a serine in v-K-ras, and in both cases the Aladdin residue at position 59 is changed to a threonine. The biological significance of these double mutations remains unclear, because mutation at position 12 alone or 59 alone is activating. Past studies have shown that these retroviral ras proteins have reduced GTPase activity, normal GDP/GTP binding, and transforming activity. These mutants also possess autophosphorylation activity at this threonine residue. However, the biological and biochemical consequences of phosphorylation in these proteins have not been addressed experimentally.

This project is investigating the function of biological activity of phosphorylation of v-H-ras oncogene proteins. To understand the role of the mutation at codon 59 and its phosphorylation, plasmids are constructed containing genes for Harvey ras: p21 (Gly-12, Thr-59) and P21 (Val-12, Thr-59). *Escherichia coli* expressed proteins and their respective phosphorylated (Pi) and nonphosphorylated (non-Pi) proteins are purified. GTPase, autophosphorylation, and nucleotide exchange activities of the mutants are studied. The mutants are microinjected into *Xenopus* oocytes to study their biological activities. These results suggest the role of phosphorylation on ras proteins. A structural interpretation of the observation is made after the crystal structures are determined for the mutants. (RPIS 3510)

427. Multiluser Crystallography Facility*S.-H. Kim**(510) 486-4333***\$150,000**

The use of synchrotron radiation to elucidate the structure, and ultimately the function, of biological macromolecules has scored notable successes in the past few years, and demand for beam time at existing facilities considerably outstrips the supply. The Advanced Light Source now under construction at the Lawrence Berkeley Laboratory will be the first synchrotron radiation facility optimized for insertion devices, and it thus offers life scientists a first opportunity to capitalize on the unique features of x rays produced at a third-generation light source. The present plan is to establish a user-oriented and user-friendly resource center to provide hard x rays to several experimental stations for x-ray diffraction studies of biological molecules and molecular complexes. The resource center will use part of the x-ray beam from a variable-polarization permanent-magnet wiggler insertion device that would be built as part of a separate proposal. The central part of x-ray fan beam from this wiggler would be used for crystallography. A beamline front end, focusing optical components, new x-ray monochromators and mirrors, and several separated exposure stations are incorporated into a novel multiluser configuration. Full

implementation of the plan will require 4 years. Ultimately, this single wiggler beamline will serve up to four users in a time sharing or energy separated mode that could be profitably adapted to other facilities around the world. (RPIS 3655)

428. Biophysical Chemistry*M. Klein**(510) 486-4331***\$170,000**

This field task is directed toward an enhanced understanding of the bioenergetics and redox state of the cell and of important cellular constituents. Applications of physical techniques continue to provide the means to these ends. The project employs x-ray absorption spectroscopy, using synchrotron radiation to ascertain the oxidation state(s) of cellular sulfur, especially that of glutathione in the living cell. Preliminary results demonstrate that the precise energy and shapes of the sulfur x-ray absorption edge can distinguish among all of the oxidation states of sulfur and, in particular, among the three oxidation states of glutathione. This result has important consequences for understanding the cellular responses to oxidative insult and damage. Intimately involved in most redox mediated pathways are the ubiquitous electron transport proteins called the Ferredoxins. Although structurally quite similar, they exhibit a very large range of reducing potentials. The sulfur atoms are thought to provide the sites of variable electron density that in turn may be modulated by hydrogen bonding. The electron density at the sulfur components is determined by observation of the sulfur x-ray absorption edges, while hydrogen bonding is determined by very high resolution electron paramagnetic resonance with electron spin echo spectroscopy and ENDOR. The Advanced Light Source will facilitate these investigations. (RPIS 3274)

429. Catalytic Antibodies*P. Schultz**D. Wemmer**S.-H. Kim**(510) 486-9277***\$245,000**

Antibodies bind a wide variety of molecules with enzyme-like affinities and specificities. Moreover, because an antibody combining site can be generated to virtually any molecule of interest, the development of general strategies for introducing catalytic activity into antibodies should provide tailor-made catalysts for use in biology, chemistry, and medicine. Antibodies are being generated that catalyze stereospecific epoxide ring opening reactions and stereospecific HCN in addition to a ketone. Esterolytic antibody are being generated capable of activating prodrugs for selective delivery of chemotherapeutic agents. In addition, mechanistic studies are being performed to determine the degree to which an esterolytic antibody functions by transition state stabilization. Efforts continue toward generating antibodies with amidase activity. A related immunochemical project involves the development of new drug strategies based on antibody targeting. Finally, stabilized α -helical peptides are being designed that bind site-specifically to DNA. (RPIS 5033)

430. Biomolecular Structure Analysis by Nuclear Magnetic Resonance*D. Wemmer*

(510) 486-4318

\$285,000

This project is developing nuclear magnetic resonance (NMR) methodology and carrying out structural studies on appropriate models for biologically important molecules. It continues to use a combination of two-dimensional NMR experiments with distance-geometry and molecular mechanics programs to define the molecular structures in solution and analyze many kinetic and thermodynamic aspects of the interactions between them. Work continues on the DNA binding domains of *gd* and *TN3* resolvase in complex with their cognate DNA. NMR studies are continuing on another DNA binding protein, *FUR*, the ferric uptake regulator from *E. coli*. The studies of the dimeric form of this protein, with a total molecular weight of about 30 kD, require isotope labeling and three-dimensional NMR, which are initiated. Through cloning and expression, production of active parts of transcriptional regulatory proteins is being investigated. These systems provide information about the molecular interactions which are at a second level of gene regulation. Investigation is beginning on the hydration of DNA in solution, by measuring the extent of cross relaxation between solvent protons and those on DNA. Similar work is being carried out on RNA as well, once the experimental techniques have been mastered. ¹H NMR is used to determine the structures and conformations of protein cofactors, particularly bilin pigments from photosynthetic bacteria. Efforts continue to apply new solid state NMR techniques (together with the Pines group) in problems of biomolecular structure in ordered samples. (RPIS 4863)

Energy and Environmental Division**431. Biological X-Ray Spectroscopy Resource Center***S.P. Cramer*

(510) 486-4720

\$50,000

This project plans to build an x-ray spectroscopy beamline for structural biology at the Advanced Light Source. An elliptical wiggler insertion device illuminates spherical grating monochromator side station for soft x-rays (180-1200eV) and a crystal monochromator end station for hard x rays (1-20keV). The end stations are equipped with detectors for transmission and fluorescence mode measurements, magnets for x-ray magnetic circular dichroism, and cryostats for temperature control from 4K to room temperature. Equipment for time-resolved and site-specific x-ray absorption is also included. The Resource Center will be operated as a national facility open to all U.S. researchers with interests in structural biology. (RPIS 5654)

Materials Science Division**432. Biological X-Ray Microscopy Resource Center***D.T. Attwood*

(510) 486-4463

\$300,000

Experimental facilities for a biological microscopy resource center are to be built at Lawrence Berkeley Laboratory's Advanced Light Source (ALS), a unique source of high brightness, partially coherent soft x rays especially well suited for biological microscopy. X-ray generation is based on undulator radiation from 1.5 GeV electrons traversing a periodic magnet structure at ALS. Beamline optics and a monochromator provide tunable, narrow band radiation to two complementary microscopes: an imaging x-ray microscope and a scanning x-ray microscope. Both microscopes will use high resolution Fresnel x-ray zone plate lenses. The imaging microscope will operate in a real image forming mode, recording the entire image at the highest possible spatial resolution and in the shortest possible exposure time. The scanning microscope, which forms an image on a pixel-by-pixel basis, does so with minimal radiation dose and a spatial resolution far beyond that of visible light microscopy. Both microscopes serve a broad biological community across the nation, including university, national laboratory, and industrial researchers, who should have wide-ranging interests that span the life sciences. (RPIS 5653)

**Lawrence Livermore National Laboratory
Livermore, CA 94550****Biomedical Sciences Division****433. DNA/Scanning Tunneling Microscopy***R.L. Balhorn*

(510) 422-6284

\$150,000

Scanning tunneling microscopy (STM) and atomic force microscopy (AFM) are two new scanning probe techniques that have been used to provide structural information about surfaces and adsorbates on surfaces at atomic resolution. This project is developing STM, AFM, and related spectroscopy capabilities so they can be used to obtain physical and electronic information about the structure of DNA and other biologically important molecules at or near the atomic level of resolution. One goal is to devise new substrates and sample deposition and imaging techniques that will allow application of these microscopies to a wide variety of biological molecules and different types of macromolecular structures. Information about a variety of biological samples at three different levels of resolution will be obtained. Methods are being developed for imaging with AFM large structures such as sperm nuclei, decondensed sperm chromatin, and mitotic chromosomes isolated by flow sorting. Single- and double-stranded DNA and stable complexes between DNA and a restriction enzyme and polymerase are being imaged at an intermediate level of

resolution. DNA bases (adenine, thymine, guanine, cytosine, and analogs), small DNAs with unique conformations (small hairpin loops and single-stranded ends), and small circular peptides of known composition are being imaged at or near atomic resolution to determine which features of atomic structure are revealed by STM and AFM. Another goal is to develop a new generation of scanning probe microscope that can discriminate between different structural components in macromolecules, such as the individual bases in DNA or particular amino acids in proteins. Different spectroscopic techniques will be tested for their ability to discriminate among the four bases of DNA and among the subcomponents of various macromolecular complexes (e.g., DNA and protein). Understanding how DNA, proteins, and their subunits are imaged will put researchers in a much better position to judge how these two nanomicroscopies can best be used in future biological studies. (RPIS 5627)

434. X-Ray Holography

R.L. Balhorn

J.E. Trebes

(510) 422-6284

\$120,000

This project is developing the capabilities of Lawrence Livermore National Laboratory in soft x-ray laser technology and x-ray imaging for use in analyzing intact, unfixed, and full hydrated biological structures. The focus of this effort is split between two tasks: (1) increasing the resolution of current two-dimensional soft x-ray microscopy capabilities to 30 nm or better and (2) developing the methods and instrumentation necessary for producing three-dimensional x-ray images of gold tagged cells. An x-ray laser zone plate microscope has been constructed and is currently being used to obtain two-dimensional images of unlabeled and immunogold-labeled rat sperm nuclei at a resolution of 50 nm with single 200psec pulses of x-rays at a wavelength of 4.483 nm. Future studies will examine chromatin fiber folding and organization in mitotic chromosomes, the identification and localization of nuclear pores and DNA-replication complexes in somatic nuclei, and the motor molecule assembly in contractility systems. Sample preparation techniques to facilitate studies of DNA and chromatin packing within intact somatic and germinal cells will be developed. Initial studies are focusing on localizing immunochemically stained histone and protamine molecules and selected DNA sequences stained by in situ hybridization in fixed, dried, two-dimensional nuclei. However, the researchers' long-term goal is to develop these techniques so they can be applied to three-dimensional visualization of similar structures in living (or at least physiologically normal) cells at a resolution approaching 10 nm. This will be accomplished by extending the current two-dimensional techniques to provide three-dimensional, high resolution images using diffraction tomographic techniques. The x-ray images of the biological structures will be validated by comparing them with images obtained with optical light, atomic force microscopy, scanning tunneling microscopy, and transmission electron microscopy. (RPIS 5628)

Los Alamos National Laboratory

Los Alamos, NM 87545

Isotope and Nuclear Chemistry Division

435. Biological Neutron Scattering

J. Trehwella

(505) 667-2944

\$262,000

This project's objective is to develop a program at Los Alamos National Laboratory for the study of biological molecular structure, thus providing a basis for understanding biological function. The Los Alamos Neutron Scattering Center (LANSCE) and the strong collaborations between Life Sciences and the neutron scattering group provide unique opportunities to develop a major center in this area. The impact of advanced biological neutron scattering capabilities on understanding biochemical processes is potentially profound. Biophysicists are rapidly progressing from studying the details of individual macromolecules to needing to understand their interactions as components within large assemblies. Using neutron scattering, individual components of complex assemblies may be studied in solution, as well as in ordered arrays, by capitalizing on the different scattering properties of hydrogen and deuterium. Because of the emergence of the Human Genome Project as a major DOE initiative, more emphasis is placed on studies of the structures of chromatin and other DNA/protein assemblies related to replication, repair, and transcription. To make full use of human genome sequence information as it becomes available, it is important to learn how it is translated in a set of highly controlled and selective processes into the working units, i.e., the proteins, of a healthy individual. Structural studies of biomolecules and biomolecular assemblies, using neutron scattering in combination with other techniques, play a vital role in unravelling these important mysteries. This research applies the neutron scattering resources (at LANSCE) to the study of chromatin structure and of other DNA protein assemblies and to the development of new methods for aligning such biological assemblies for structural studies. In addition, study continues on the structures of molecules, important proteins in the immune response, in particular antibody/antigen complexes, in order to understand how differences in the protein amino acid sequences relate to differences in their biological functions. (RPIS 4664)

Oak Ridge National Laboratory

Oak Ridge, TN 37831

Biology Division

436. Structural Biology of Nucleosomes

G.J. Bunick

(615) 574-2685

\$275,000

The goal of this structural biology research program is to investigate the three-dimensional structures of important biological macromolecules. A major objective is to determine

a higher resolution crystal structure of the nucleosome core particle. One or more crystal forms obtained by crystallizing nucleosomes reconstituted from purified histones and specific sequence DNA are solved to a resolution of ~3 angstrom using synchrotron radiation and heavy-atom derivative multiple wavelength anomalous diffraction phasing. This research may provide atomic resolution information, which is of fundamental importance to a detailed understanding of gene expression and the structures of DNA and chromatin. In conjunction with and complementary to the crystallographic work, studies are being initiated to obtain dynamical information concerning the functional relationships between structural elements within the 30 nm chromatin fiber. These studies utilize neutron scattering and a viscous shear alignment system at Oak Ridge National Laboratory. The 2.3 angstrom resolution x-ray crystal structure of inorganic pyrophosphatase, an enzyme that drives nucleic acid and fatty acid biosynthesis reactions to completion, is undergoing crystallographic refinement by simulated annealing. Two other proteins, epidermal growth factor and O6-methylguanine-DNA methyltransferase, are subjects of crystallization experiments. Experiments are defining the crystallization conditions of phosphoribulokinase. (RPIS 5093)

437. Chromosome Chemistry

D.E. Olins

(615) 574-1265

\$115,000

The purpose of this research is to understand the structure of eukaryotic chromosomes during DNA packaging, transcription, and replication. An anticipated benefit is an understanding of normal and abnormal chromosome functioning. The technical approach combines molecular biology and light and electron microscopy. The principal experimental system of study is a protozoan, *Euplotes eurystomus*, whose macronucleus (MAC) has two unique advantages: (1) the MAC genome is amplified into short linear DNA molecules (ca. 2 kbp), single genes terminated by telomeres, is associated with histones, and is folded into oligonucleosomal minichromosomes. Specific genes have been sequenced, and the positions of nucleosomes determined. (2) MAC DNA replication occurs in a migrating organelle, the replication band (RB). Components of the RB are identified, and their localization and regulation understood. The higher order nuclear structure is studied. To elucidate the higher order arrangement of eukaryotic chromosomes, electron microscope tomography (EMT) has been developed to accomplish three-dimensional reconstructions of asymmetric cell structures in plastic sections. Developments in EMT include (1) visualizing thick sections with inelastically scattered electrons using electron spectroscopic filtering, (2) employing a selective electron-dense stain for DNA, and (3) developing highly interactive three-dimensional computer graphics techniques. (RPIS 0284)

Stanford Linear Accelerator Center Stanford, CA 94309

Stanford Synchrotron Radiation Laboratory

438. Structural Molecular Biology Support Initiative

K.O. Hodgson

(415) 926-4100

\$250,000

Synchrotron radiation provides unique capabilities that are very relevant to structural studies in molecular biology. Stanford Synchrotron Radiation Laboratory (SSRL) has programs in structural molecular biology research that utilize x-ray crystallography, x-ray small angle scattering, and x-ray absorption spectroscopy. This project provides increased access and support for structural molecular biology users of the SPEAR storage ring at SSRL, to develop new instrumentation for structural molecular biology research using synchrotron radiation, to develop advanced computing algorithms for data analysis and graphic display, and to develop a new beam line (Beam Line 9) for such research on SPEAR. Further expanded space provides support for auxiliary needs of structural molecular biology users at SSRL. (RPIS 5385)

Biotechnology: Structural Biology

Offsite Grants

University of California, Berkeley Berkeley, CA 94720

Department of Chemistry

439. Structure and Stability of Nucleic Acids

I. Tinoco, Jr.

(510) 642-3038

\$300,000

The goals of this research are to determine the thermodynamics, kinetics, and structures of different ribonucleic acid (RNA) and DNA conformations and to relate them to the biological functions of the molecules. Investigators have determined the first atomic resolution structure of an RNA hairpin in solution. One- and two-dimensional nuclear magnetic resonance (NMR) measurements were done to determine the structure of the hairpin of 12 nucleotides. One of the most important aspects of the loop structure is the occurrence of a G•U base pair in which the guanine has a *syn* conformation at the glycosidic bond instead of the usual *anti* conformation. The *syn* base may explain why reverse transcriptase and 3' exonucleases have difficulty in traversing the loop. A second important aspect of the loop structure is the fact that the second base of the loop has no specific interactions with the rest of the loop. This fact

explains why in ribosomal RNAs (rRNAs) this is the most chemically reactive base in the loop and why any base can substitute here in different rRNAs.

The structure of one class of RNA pseudoknots has been determined using NMR. The pseudoknot consists of two contiguous stems coaxially stacked and two adjacent loops attached. The pseudoknot structure is stable when the first loop contains at least three nucleotides and the second loop contains at least four nucleotides. Pseudoknots cause frameshifting during translation of messenger RNA, but the structural reason for this is not obvious.

The applications of NMR methods are being extended by using ^{13}C -labeled and ^{15}N -labeled molecules. This procedure allows atomic resolution structures for RNA molecules containing 20–40 nucleotides. (RPIS 9473)

University of California, Davis

Davis, CA 95616

Department of Biological Chemistry

440. Neutron Scatter Studies of Chromatin

E.M. Bradbury
(916) 752-2929

\$273,000

To understand chromosome structure/function relationships, it is necessary to assemble nucleosomes and chromatin that are fully defined with respect to DNA sequence, histone subtypes, histone modifications, and nucleosome positions. This assembly has been achieved, and researchers are now able to determine the structure/function relationships of chromatin variables. Initial neutron scatter studies of assembled nucleosomes have shown that the DNA coiled around the histone octamer is longer than the 146 bp DNA found for the core particle. This finding has implications for the function of histone acetylation, which is strictly correlated with transcriptional activity. It has been shown in closed circular minichromosomes that hyperacetylation of histones H3 and H4 reduces the nucleosome linking number change from 1.04 to -0.81. Thus, histone acetylation is able to release negative DNA supercoils, previously constrained by the nucleosome into chromosome loops. The DNA constructs used in these assembled nucleosomes contain—in addition to nucleosome locating sequences—a DNA binding site for transcription factor TFIIA. Contrary to proposed models, the researchers find that TFIIA induces an approximately 60° bend in the DNA binding site, and this finding is supported by initial neutron scatter studies of the TFIIA/DNA complex. The groundwork for the next phase of understanding chromatin structure/function relationships has been laid. (RPIS 9726)

University of Chicago

Chicago, IL 60637

Enrico Fermi Institute

441. Electron Microscope Development

A.V. Crewe
O.H. Kapp
(312) 702-7821

\$275,000

This project continues work on theoretical electron optics, instrument construction, and biological research focused on the hemoglobins of the invertebrates. Work is also continuing in electron optics with special emphasis on the simultaneous correction of spherical and chromatic aberrations using electron mirrors. New systems are being designed, and the researchers hope to proceed with their construction. The biological work places special emphasis on the hemoglobins of the invertebrates, particularly the hemoglobins of the oligochaete and polychaete worms. Improvements are being made on the three-dimensional reconstruction algorithms, and work focuses on different representation schemes (shading, etc.) for optimal display of data. Low-Z support films are being investigated in an attempt to relate microscope data to crystallography data. In addition, software is being developed to perform alignment of amino acid sequences in two and three dimensions. (RPIS 9523)

Princeton University

Princeton, NJ 08544

Physics Department

442. Development and Applications of Photo-Sensitive Device Systems to Studies of Biological and Organic Materials

S.M. Gruner
(609) 258-4334

\$272,000

The objectives of this program are to develop and apply instrumentation and new experimental techniques to studies of biological and polymeric materials. Specific ongoing instrumentation programs are (1) the development of advanced two-dimensional electro-optical x-ray detectors and ancillary apparatus, especially as required for the high flux radiation encountered at synchrotron radiation sources and (2) methods of low level imaging light detection. The x-ray instrumentation aspects of the program involve investigation of detectors, beam line instrumentation, time-resolved diffraction methods, and study of the materials and thermodynamic properties of biomembranes, liquid crystals, and polymers. Recent research problems to which the x-ray equipment have been successfully applied include biomembrane phase transitions, biomembrane protein function, membrane encapsulated drug delivery, the behavior of novel surfactants, and the structure of block copolymers. The x-ray equipment developed for this research

is being installed at a number of synchrotron beam lines. The low light level detection aspects of the program involves investigations of instrumentation and techniques for low light microscopy and spectroscopy to the study of bioluminescent and chemiluminescent systems and research into lyoluminescent radiation dosimetry. (RPIS 9643)

Rice University
Houston, TX 77252

Department of Physics

443. Quasi-Elastic Neutron-Scattering Studies of Protein Dynamics

H.E. Rorschach
(713) 527-8101

\$36,000

The techniques of x-ray and neutron scattering have been applied in the past to the study of the thermal motion of the atoms in biological molecules. These techniques employ diffraction methods and make use of large single crystals. It is assumed that the results are representative of the molecular motion in solutions. This may be true for the interior of the molecule, but it is not obvious that it holds for the outer layers. In addition, the low frequency motion (diffusion, hinge-bending), which may be important for enzymatic reaction rates, cannot be studied by this method.

This project is studying the molecular dynamics of the protein trypsin by the method of quasi-elastic neutron scattering, a method which can be used to determine both the high frequency and diffusive motion in powders, single crystals, and solutions. Information is obtained on the dynamics, free of the influence of defects as a function of hydration, so that the onset of the low frequency diffusive motion can be traced. The study of this low frequency motion is very important for a full understanding of the dynamics of proteins in solutions. It is also important for an understanding of the water-protein interaction, which plays an essential role in the nuclear magnetic resonance imaging process. (RPIS 9914)

State University of New York at Stony Brook

Stony Brook, NY 11794

Department of Physics

444. X-Ray Micro-imaging by Diffractive Techniques

J. Kirz
(516) 632-8106

\$380,000

This project is developing high resolution x-ray micro-imaging techniques for the study of wet biological specimens using the X1A undulator beamline at the National Synchrotron Light Source. The beamline is about to be upgraded to provide a fivefold increase in throughput. This added capability allows the development of (1) techniques to combine small angle

scattering from submicron areas with direct imaging; (2) methods to reduce radiation damage, especially for multi-wavelength imaging; (3) high resolution readout of Gabor holograms using a specially designed atomic force microscope; (4) charge coupled device-based detection of large angle diffraction patterns from noncrystalline specimens, and (5) techniques to exploit the additional increase in brightness expected at the Advanced Light Source, under construction at the Lawrence Berkeley Laboratory. (RPIS 10322)

Biotechnology: Medical Applications

Intramural DOE Laboratories

Argonne National Laboratory

Argonne, IL 60439

Chemistry Division

445. Research in Nuclear Medicine

R.W. Atcher
(708) 252-6728

\$410,000

This program's primary objective is the development and testing of radiolabeled pharmaceuticals for use as therapeutic tools. The program focuses on the basic nuclear and radiochemistry required for the production and synthesis of certain compounds. Fundamental studies are performed of the biological effects of the compounds. These studies are done in collaboration with members of the Biological and Medical Research Division of Argonne National Laboratory and other public and private institutions. After a project advances to the clinical stage, funding is sought from other sources to support more applied research leading to clinical evaluation. Areas of concentration are on radiopharmaceuticals of use in radionuclide therapy and radiopharmaceuticals of potential use in receptor-based imaging. (RPIS 1457)

Brookhaven National Laboratory

Upton, NY 11973

Biology Division

446. Radioactive Gold Clusters Bound to Tumor Antibodies for Cancer Therapy

J.F. Hainfeld
L.F. Mausner
(516) 282-3372

\$205,000

A new method has been developed to covalently link stable clusters of gold atoms to antibodies and antibody fragments in such a way that full antigenic specificity and capacity are

preserved. Although existing methods for attaching radioactive atoms to antibodies are sometimes adequate for diagnostic imaging, sensitivity is limited by the small number of atoms that can be attached before antibody specificity is reduced or lost. This same constraint limits the radioactive dose that can be delivered to tumor cells in radioimmunotherapy. By use of atom cluster compounds, 11 (and perhaps 55) gold atoms can be covalently attached as an entity at a site on the antibody, which is at the opposite end of the antigen combining region. This should allow preservation of immunological activity of the antibody. Gold-199 (^{199}Au) is an attractive therapeutic radionuclide because of its 3.1-day half-life, intermediate energy beta (β) emission, and imageable gamma (γ) ray. Gold-199 labeled antibodies can be made with high specific activity for more effective radioimmunotherapy. In preliminary work, researchers have successfully linked a monoclonal antibody raised against human colon carcinoma to an 11-gold atom cluster (using radioactive gold). Cell-binding assays showed good retention of immunospecificity. A cluster with similar chemical properties having 55 gold atoms is being developed to further enhance dose delivery. The purpose of this research is to develop the chemistry of these immunoconjugates with high specific activity ^{199}Au . The labeled immunoconjugate will be tested in vitro and in vivo with nude mice to establish the feasibility of this approach and demonstrate its expected advantage over conventional techniques. (RPIS 5284)

Chemistry Department

447. A Regional Cyclotron-Positron Emission Tomography Center for Radiotracer Research and Medical Application

A.P. Wolf
J.S. Fowler
S. Dewey
R.F. Ferrieri
J.S. Gatley
A. Levy
D.J. Schlyer
(516) 282-4397

\$1,500,000

This program focuses on the development and application of short-lived positron emitters to new problems in biology and medicine. Historically, it has made fundamental contributions to radiotracer research, ranging from the measurement of excitation functions to the development of specific positron emission tomography (PET) methods to probe biochemical transformations in humans. Advances in radiotracer chemistry, especially the development of new, high-specific-activity syntheses with carbon 11 and fluorine 18, have resulted in synthetic methods and mechanistic approaches to radiotracer design and evaluation that are widely applied in PET centers throughout the world.

Over the past 3 years, a number of significant new research directions has emerged from this program. These focus mainly on research in the neurosciences and include (1) the use of a multitracers, longitudinal approach to studying the effect of

cocaine abuse on the dopaminergic system (with Nora Volkow, Brookhaven National Laboratory Medical Department); (2) the first investigations of the use of PET to study neurotransmitter interactions; (3) the development of the first high-specific-activity fluorine 18-labeled catecholamines for examining neuronal activity in the heart; and (4) the use of PET to study therapeutic drugs, especially for the treatment of neurological and psychiatric disease. Tracer kinetic modeling strategies are being developed and applied to PET data with special interest in developing methods for quantitating relative changes in neurotransmitter concentration. A commitment to developing new image analysis strategies has been initiated. Our long-standing interest in the production of medically useful radio-isotopes of iodine continues with significant advances in the development of new methods for the production of iodine 123 and iodine 124. Research also addresses automation and robotics, not only for radiotracer synthesis but also for measuring plasma input function for tracer kinetic analysis of PET data. Training and technology and information transfer remain as strong commitments and Brookhaven National Laboratory will continue to serve as a resource for training in response to the needs of new cyclotron-PET centers. (RPIS 2282)

Medical Department

448. Joint Proposal for Neutron Capture Therapy

R.M. Brugger
(516) 282-3625

\$850,000

First, for neutron capture therapy (NCT) to become a successful therapy, a beam with appropriate energy neutrons must be available. Second, a boron-carrying compound that concentrates enough boron in the tumor target while bypassing healthy tissue must be identified. At the Brookhaven Medical Research Reactor (BMRR), an epithermal neutron beam has been installed that is suitable for clinical NCT of choroidal melanoma of the eye and of malignant glioma of the cerebrum. A thermal neutron beam also is available for NCT of cutaneous melanoma. The physical and the biological dosimetry for these two beams is being refined. This dosimetry is being coupled to programs for treatment planning to provide the necessary interconnections for starting therapy.

Several boron-containing compounds have been identified as promising for NCT. At least three compounds can be used to cure or control highly malignant, lethal melanomas and gliomas in mice and rats. A major purpose of this project is to identify and perform animal and human studies that will demonstrate the effectiveness of these compounds and will lead to the most effective clinical uses of NCT at BMRR.

This project, which is devoted to the clinical implementation of NCT, coordinates these research facilities with clinical facilities and personnel at two collaborating major medical centers, The Ohio State University and The State University of New York at Stony Brook. Within the next year, the project will initiate programs for clinical investigations of NCT at the epithermal beam port. (RPIS 4897)

449. Clinical Feasibility of Boron Neutron Capture Therapy Using p-Boronophenylalanine*J.A. Coderre**(516) 282-2298*

\$222,000

The long-term goal of this project is to develop boron neutron capture therapy (BNCT) into a clinically useful method of radiation therapy for human tumors. Experimental BNCT focuses on an intracerebral rat gliosarcoma (using thermal neutrons) and a melanoma in the posterior segment of the rabbit eye (using epithermal neutrons) following systemic administration of the boron-containing amino acid p-boronophenylalanine (BPA). Effective tumor control with little or no damage to immediately adjacent normal tissue is demonstrated. The extent to which normal tissues are damaged during BNCT is quantified and compared to the damage produced by conventional photon irradiation. The effectiveness of fractionated BNCT irradiations is being investigated. The Phase I clinical trial is being continued (biodistribution study). Optimization of BPA delivery proceeds along the lines shown to be effective in the animal tumor models: larger, single oral doses or multiple oral doses. The demonstration of effective tumor therapy and the results of the normal tissue tolerance studies in the rabbit eye and rat brain tumor models, in conjunction with the human BPA biodistribution studies, provide all of the information necessary for starting BNCT irradiations of human brain tumors or human ocular melanoma. (RPIS 5277)

450. Multiple Energy Computed Tomography for Neuroradiology with Monochromatic X Rays from the National Synchrotron Light Source*F.A. Dilmanian**(516) 282-7696*

\$535,000

Monochromatic x-ray beams from the X-17 Superconducting Wiggler of National Synchrotron Light Source are used to carry out in vivo multiple energy computed tomography (MECT) of the human head and neck. The computed tomography (CT) configuration is that of a fixed, fan-shaped beam in a horizontal plane and a rotating, seated subject. The in-plane spatial resolution is 0.5 mm full-width-at-half-maximum. MECT is used in two modes: (1) dual-photon absorptiometry (DPA) CT, in which the subject is imaged at two well-separated energies (e.g., 40 and 100 keV) to obtain two images highlighting the concentrations of the low-Z and the intermediate-Z element groups; and (2) K-edge subtraction (KES) CT of contrast elements, such as iodine, in which the subject is imaged just above and just below the K-edge of the contrast element. These images are logarithmically subtracted. Calculations show that the improvements obtained in image sensitivity and image quantitative accuracy in both DPA and KES CT are substantial compared to conventional CT because of the lack of beam hardening and the effect of fine energy definition on the DPA and KES CT image quality. The clinical research program planned for the system includes using DPA CT to image ischemic lesions and atherosclerotic plaques and using KES CT to image tumors and the lumen of the major arteries of the head and neck. (RPIS 5048)

451. Evaluation of Boron Compounds for Neutron Capture Therapy*D.D. Joel**(516) 282-3603*

Research continues in examining certain variables in boron neutron capture therapy (BNCT) using rats bearing intracerebral gliosarcomas as a model of human malignant gliomas. The therapeutic efficacy of BNCT was clearly demonstrated in this model with two separate 10B-carriers, namely, sulfhydryl borane dimer ($\text{Na}_4^{10}\text{B}_{24}\text{H}_{22}\text{S}_2$) and 10B-boronophenyl alanine. Preliminary results suggest, however, that the mechanisms of tumor control following BNCT may depend upon the specific 10B carrier used. These different mechanisms are elucidated using in vivo and in vitro techniques.

The effects of glutathione monoesters on tumor boron uptake and retention in tumors, and the efficacy of BNCT associated with the administration of the sulfhydryl boranes, monomer (BSH) and dimer, continue to be studied. These studies have important clinical significance because BSH is likely to be the first compound used in the treatment of malignant brain tumors with BNCT.

The effectiveness of BNCT depends, in part, upon the microdistribution of 10B in tumor and surrounding tissues and cells. Further development and refinement of a high resolution immunofluorescence technique to detect 10B carriers at the cellular level are proposed. With the use of animal models, analysis of the radiobiological and dosimetric criteria for BNCT of brain tumors continues. An important question is whether brain tumors can be cured in the absence of late-delayed radiation necrosis of the brain. Testing the toxicity and biodistribution of other 10B carriers, particularly the boronated porphyrins, also continues.

It is anticipated that these studies will yield information to aid in establishing a scientifically sound approach to clinical trials of BNCT of human malignant brain tumors. (RPIS 4784)

452. Synthesis of New Rigid Chelating Agents for Preparing Stable Radiometal Immunoconjugates*R.C. Mease**(516) 282-4865*

\$175,000

The primary goal of this project is to synthesize new chelating agents that produce radioimmunoconjugates with higher in vivo stability. The new chelates have ethylene diaminetetraacetic acid and diethylenetriaminepenta-acetic acid molecules incorporated into the rigid carbon backbone of bicyclo[2.2.1]heptane and bicyclo[2.2.2]octane. The rigidity of the carbon backbone locks several ligand-coordination sites into positions that favor metal chelation. At the same time, by inhibiting the approach of competing in vivo ligands, the steric bulk of the backbone confers greater stability upon the chelate. Acidity constants and metal-chelate formation constants are measured for the new ligand systems. Promising new ligands are modified synthetically at a position remote from the metal-complexing region to allow their conjugation to antibodies. The new radioimmunoconjugates are tested for biodistribution in nude mice with tumor xenografts. (RPIS 5276)

453. Physiological Targeting of Stable and Radioactive Isotopes to Tumor for Radiotherapy

D.N. Slatkin

(516) 282-3185

\$460,000

This project is for the support of experimental and, in part, clinical investigations designed (1) to improve radiation for primary and metastatic brain tumors and (2) to minimize the toxic effects of combined radiotherapy/chemotherapy for brain tumors. These studies are mainly on boron neutron capture therapy (BNCT), but work on radioiodinated iodothiouracil therapy for systemic melanotic melanoma is also pursued.

In BNCT, studies with a new boronated porphyrin, VCDP, focus on its hematologic, hepatic, and possible cerebellar toxicities in mice, rats, and rabbits. Unenriched and ^{10}B -enriched VCDP is synthesized for experimental BNCT of an intracerebral rat gliosarcoma. The synthesis of a carboranylated radiographic contrast agent as a slow neutron target compound for BNCT that potentially can be imaged by x-ray computed tomography and, in its radioiodinated form, by single-photon emission computed tomography or by autoradiography is studied. The method of deuterium-hydrogen exchange is used to determine conditions for synthesis of high-specific-activity tritiated borane monomer and dimer for ^3H autoradiography. Studies on cerebellar radiotoxicity continue, with the use of ^{10}B -enriched boric acid with the $^{10}\text{B}(n,\gamma)\text{Li}$ reaction to preferentially irradiate the cerebellar endothelium. X-irradiation is used to irradiate the cerebellar parenchyma and vasculature equally. The research explores the differential radiation protective effect for low- and high-LET radiations of a radiation protective agent (RPA) that penetrates the blood-brain barrier poorly, such as WR 2721, and of the putative RPA, glutathione monester, which may enter the brain parenchyma more freely. The testing of BNCT-candidate boronated compounds in vitro continues to fulfill previous commitments. (RPIS 4187)

454. Radionuclide and Radiopharmaceutical Research for Medicine

S.C. Srivastava

(516) 282-4459

\$880,000

This program covers many fundamental aspects of radionuclide and radiopharmaceutical research leading to new and more effective diagnostic and therapeutic agents. The research includes collaborative projects with many onsite and offsite DOE-supported programs. Many unique Brookhaven National Laboratory facilities are used, including the Brookhaven Linac Isotope Producer (BLIP), the High Flux Beam Reactor, the Brookhaven Medical Research Reactor, cyclotrons, high level radiation processing cells, and the laboratory animal and clinical facilities. The value of BLIP to the nuclear medicine community is well established; the renovated facility has continued to serve as a unique source for research on new, medically useful radionuclides. Production and distribution of routine isotopes to industry is now a separate project and no longer part of this program.

The long range project objectives are to (1) design, develop, and evaluate new radiopharmaceuticals that provide higher specificity and sensitivity in diagnosis and therapy and that aid in the quantitative assessment of biochemistry and physiology through functional imaging; (2) identify and develop new optimum radionuclides that meet these goals for specific applications and carry out nuclear cross-section studies, targetry research, and development of radiochemical and radioanalytical procedures (recent examples: ^{47}Sc , ^{64}Cu , ^{67}Cu , ^{97}Ru , ^{96}Tc , ^{117}mSn , ^{199}Au , and ^{203}Pb); and (3) provide these or other commercially unavailable radionuclides for DOE-supported onsite and offsite collaborative research. The recent major emphasis in this program has been in research on radio-labeled monoclonal antibody immunoconjugates for both imaging and therapy, blood cell labeling techniques and mechanisms, and development of new radiopharmaceuticals for oncology and for cardiovascular and brain single-photon emission computed tomography imaging. Extensive nuclear and radiochemical studies, development of radiosynthetic and analytical procedures, ligand synthesis, mechanistic investigations, animal studies, and preliminary clinical trials are integral parts of this program. (RPIS 1159)

455. Radioimmunoconjugates of Antiplatelet Monoclonal Antibodies from Thrombus Imaging

S.C. Srivastava

P. Som

(516) 282-4459

\$280,000

This research investigates the potential of labeled antibodies and laminin peptides as receptor-binding molecular probes for imaging arterial and venous thrombi and inflammation. Earlier, it was demonstrated that in dogs, thrombi could be imaged using a human antiplatelet monoclonal antibody (7E3) labeled with ^{111}In or ^{123}I . It was also shown that thrombi could be imaged using a $^{99\text{m}}\text{Tc}$ labeled fragment mixture of another antiplatelet antibody, 50H.19, and that thrombosed bowel could also be imaged with this technique. Further work is needed to improve the in vivo stability of these labeled conjugates for use in clinical studies. Emphasis is on optimizing labeling chemistry for attaching $^{99\text{m}}\text{Tc}$ using the bifunctional chelate approach. The rigidity of the chelating agents, methods of conjugation, degree of substitution, and the nature of reducing agents are evaluated for the best in vitro and in vivo performance. A number of ligands for optimization of $^{99\text{m}}\text{Tc}$ labeling is available from the synthetic efforts in other current projects.

These investigations include a new approach using peptide subunits that bind to integrin-type receptor sites on platelets and activated white cells. Preliminary work has shown that this approach is feasible using a $^{99\text{m}}\text{Tc}$ -labeled laminin nonapeptide, which has a high affinity for human and dog clots and platelets. This approach may prove more advantageous in some situations than the use of monoclonal antibodies. Biodistribution and kinetics of $^{99\text{m}}\text{Tc}$ immunoconjugates are compared with those of the $^{99\text{m}}\text{Tc}$ peptides in animal models of experimental thrombi and inflammation using quantitative autoradiographic microimaging and planar and single-photon emission

computed tomography. These studies provide information on the molecular mechanisms in these disease states and thus permit a systematic development of the best ^{99m}Tc -labeled agent(s) for imaging thrombi and inflammation. (RPIS 5035)

456. Positron-Labeled Monoclonal Antibodies for Positron Emission Tomography Imaging Studies

S.C. Srivastava

(516) 282-4459

\$246,000

This research develops new radioimmunoconjugates for positron emission tomography (PET) imaging. Due to the advantages of PET in resolution, quantification, and sensitivity, development of positron-labeled monoclonal antibodies leads to new agents, not only for imaging and quantification of tumors but also for studies clarifying the biochemistry of these diseases. In addition, quantitative volume measurements of radionuclide distribution are useful in calculating radiation dose before radioimmunotherapy. Initial efforts use three specific monoclonal antibodies (whole IgG and fragments): (1) anticolon carcinoma antibody, 17-1A; (2) anticancer embryonic antigen antibody; and (3) antiglioma antibody, EGF-425. The nuclides used initially include ^{18}F , ^{55}Co , and ^{64}Cu . These can be produced by the unique Brookhaven Linac Isotope Producer, High Flux Beam Reactor, or facilities at the Chemistry Department. Emphasis is placed on the development of novel ligands and new methods of immunoconjugation. Research is carried out jointly between the Medical and Chemistry Departments. Experience at Brookhaven National Laboratory with positron-labeled radiopharmaceuticals and radiolabeled monoclonal antibodies, coupled with the state-of-the-art nuclide production capabilities and PET imaging equipment, provides a unique environment for the investigations. (RPIS 5047)

457. PET Research in Substance Abuse

N.D. Volkow

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\$560,000

In close collaboration with the Chemistry Department at Brookhaven National Laboratory and the State University of New York at Stony Brook, positron emission tomography (PET) is used in conjunction with different radiotracers to investigate mechanisms of toxicity of drugs of abuse and to assess the metabolic and neurochemical changes associated with drug withdrawal and addiction. Studies focus on two of the most problematic drugs of abuse: cocaine and alcohol. In the studies on cocaine, the focus is upon the investigation of the pharmacological properties of cocaine in the human brain and body and on the consequences of chronic cocaine use on brain metabolism and neurochemistry as they pertain to cocaine withdrawal and addiction. The studies on alcohol focus on evaluating regional brain metabolic changes secondary to chronic use of alcohol and on assessing the contribution of alcohol withdrawal on these changes. In addition, it is determined whether alcoholics show abnormal inhibitory neurotransmitter function that could explain their use of ethanol.

In parallel to the studies on substance abuse, PET was used in conjunction with different radiotracers to identify cancer types for which PET may be uniquely useful in diagnosis and evaluation. (RPIS 5369)

458. Medical Applications of Nuclear Technology

D.A. Weber

(516) 282-7765

\$1,335,000

The nuclear medicine program develops new and improved nuclear medicine procedures for the study of human health and disease. Major emphasis is placed on developing more quantitatively accurate single-photon emission computed tomography (SPECT) imaging methods and using this technology and associated imaging methods to develop new procedures. Experimentally validated Monte Carlo simulation studies are used to investigate scatter-media-dependent properties of the Compton-scattered photons in uniform and nonuniform distributions of lung, bone, and muscle (water) tissue. The energy-, depth-, and density-dependent scattered photon distribution functions obtained in these studies provide the information needed to develop new reconstruction algorithms to reduce the Compton scatter component in SPECT images. These reconstruction algorithms should yield images with improved spatial resolution and more accurate quantitation of activity. Quantitative SPECT and associated imaging methods are applied in preclinical and clinical studies to investigate the influence of the addictive and toxic effects of cocaine. Quantitative autoradiography and specimen assays are used to investigate the target organs of cocaine and the receptor sites influencing its localization: SPECT and planar gamma camera images (whole body and regional) are used to study target organ pathology, perfusion, and metabolism in acute and chronic uses of cocaine. Collaborative studies involve preclinical and clinical studies with new and established SPECT imaging agents and radiopharmaceuticals used for therapy.

Reactor Division

459. Brookhaven Medical Research Reactor Operations

M.H. Brooks

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\$1,115,000

The Brookhaven Medical Research Reactor (BMRR) is a 3-MW research reactor, constructed primarily for medical and biological research. This proposal provides the funding required for the operation and maintenance of the reactor facility in support of preclinical studies designed to facilitate initiation of clinical trials of neutron capture therapy (NCT).

Although BMRR has the capability for isotope production and activation analysis, its two primary facilities are designed to provide intense neutron beams for patient irradiations in the NCT procedure. Current studies are directed toward the implementation of the epithermal and neutron beam for clinical trials of NCT. An epithermal neutron beam has been installed, which has the capacity to deliver a therapeutic irradiation in 30-60 minutes with fast neutron and gamma contaminations

low enough that the beam is satisfactory for therapy. A study has been started to identify ways to enhance the effectiveness of this beam.

Operation of the reactor is managed by the Brookhaven National Laboratory Reactor Division in accordance with DOE Order 5480.6, Safety of DOE Owned Nuclear Reactors. At present, maximum allowable power is 3 MW, although limited operations at power levels up to 5 MW have been authorized in the past. Clinically useful operation would be enhanced if this limit were increased to 5 MW. (RPIS 5223)

Idaho National Engineering Laboratory

Idaho Falls, ID 83415

New Program Development

460. Boron Neutron Capture Therapy Research Program

R.J. Wiersema

(208) 526-9264

\$3,000,000

This multi-institutional research program is developing a treatment modality for cancer using the Boron Neutron Capture Therapy (BNCT) protocol. Included in the research activities are drug development and investigations of the pharmacokinetics of boron compounds in suitable animal models. Work consists of the following areas of activity:

(1) Developing analytical tools and computer software necessary to carry out this program.

(2) Developing boron-containing drugs, including screening, toxicity, and interaction studies.

(3) Conducting a small and large animal program to assess boron uptake, pharmacokinetics, and toxicity and to establish a boron drug final dosage form.

(4) Conducting a canine tumor treatment program to ensure safety and maximize efficacy of the BNCT procedure.

(5) Developing neutron sources suitable for clinical trials.

(6) Developing an international collaborative exchange program with the European Collaboration of BNCT and the Japanese and Australian BNCT programs. (RPIS 5034)

Lawrence Berkeley Laboratory

Berkeley, CA 94720

Cell and Molecular Biology Division

461. Clinical Heavy Ion Radiobiology

E.A. Blakely

J.R. Castro

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\$260,000

The clinical research trial in charged-particle radiotherapy, which uses heavy ion beams accelerated at the Lawrence Berkeley Laboratory BEVATRON/BEVALAC facility, has had considerable success in treating a wide array of tumor types in different locations of the body. Prospective randomized trials

are under way to confirm improved local control and survival compared to historical data from treatments with conventional radiation modalities. A key element in the successful implementation of charged-particle therapy is the requirement for in vitro heavy ion biological dosimetry. To conform the high dose treatment volume to each patient's tumor, ion beams of different types, depths of penetration, and of different field sizes are required. The variables of particle atomic number and energy and the techniques used to enlarge the beam field may significantly alter the biological effects in the patients because of beam fragmentation and scattering processes that can change the effective linear energy transfer (LET) value of the composite beam. Ionization chambers are not adequate to measure the LET differences. Solid-state silicon-germanium detectors have been built at LBL to measure LET. However, the sensitive volumes of the detectors are small, and they cannot be routinely used for large exposure fields. Biological systems such as human fibroblasts in culture are sensitive to the LET differences. Although the single-dose relative biological effectiveness (RBE) data for clonal survival are not absolutely "correct" for human tissue, these data are consistently proportional to human skin RBE data for acute dose reactions and surprisingly close in numerical values. It is the relative changes in cell-killing effects determined with these cellular techniques that provide the quantitative basis for patient filter design and input into the treatment planning model. These cell data are then modified by known data such as for skin, mucosa, central nervous system, and gastrointestinal tissues available from studies in animals and humans. The biological dosimetry support is needed to fulfill the ongoing need for verification of biological effects of new beam configurations, including new treatment protocols under development to compare the clinical usefulness of helium ions, neon ions, and silicon ions. In addition, a new method of beam delivery called raster scanning is being developed, which will permit a more accurate painting of the dose on the tumor target. Implementation of this technique in clinical practice cannot be done with safety until appropriate biological screening and evaluation of dose rate effects is accomplished. A 5-year plan has been designed to obtain the radiobiological information necessary to optimize the clinical applications of charged-particle radiotherapy in three dimensions. Additional studies on tumor biopsy material may contribute to future patient selection procedures. (RPIS 5370)

462. Diagnostic Use of High Energy Radioactive Beams in Cancer Therapy and Nuclear Medicine

A. Chatterjee

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\$90,000

The immediate goal of this research is to provide a technique that can be used routinely as a diagnostic procedure for localizing the Bragg peak (maximum ionization and maximum cell killing) on the tumor volume in cancer therapy with heavy ions. The approach is based on the use of high energy radioactive beams (which decay by emitting positrons) produced as secondary particles from the BEVALAC. These particles have

penetration properties similar to those of the nonradioactive therapy beams; hence, a measurement of the stopping region of the secondary beams through positron imaging can provide the information necessary for the required adjustment of the incident energy of a beam of heavy charged particles with which a patient is going to be treated. A special positron camera called PEBA is available and is capable of locating the stopping region with an accuracy of ± 1 mm. Through proper adjustment of the energy of a radioactive beam, the stopping point can be controlled to coincide with the location of a tumor volume; through an appropriate scaling of the atomic and mass numbers between the secondary beam and the primary beam, the Bragg peak can be precisely (± 1 mm) positioned on the tumor volume for the therapy beam. The radioactive beams suitable for these studies are neon-19 and carbon-10 for the corresponding therapy beams neon-20 and carbon-12. Improvement of the software associated with imaging is continuing. The present algorithm for the construction of image is being modified in order to acquire a better sensitivity. Preliminary phantom experiments are in the planning stage to explore the usefulness of high energy radioactive beams as tracers in blood flow studies. (RPIS 2417)

Engineering Division

463. Application of Statistically Based Algorithms to Emission Tomography

J. Llacer

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\$205,000

The objective of the task research is the development, evaluation, and initial application of image reconstruction algorithms for emission tomography, algorithms based on knowledge of the statistics of the emission and detection processes and the a priori statistical, medical, and perceptual knowledge available at the time of the reconstruction. The work uses as a foundation the excellent results of Maximum Likelihood Estimator reconstructions using the concept of "feasibility" as a necessary condition for image acceptability, a stopping rule based on likelihood cross validation and the researchers preliminary work on Bayesian reconstructions with entropy priors. The research is being carried out in several main areas: (1) studying new methods of obtaining feasible images by use of nondeterministic reconstruction methods, like neural networks, (2) finding new ways of incorporating prior medical knowledge into the reconstruction algorithms, (3) critically evaluating the reconstructions by both mathematical characterization and through ROC studies in a clinical environment, and (4) placing a practical reconstruction capability in a clinical environment for testing the methods developed in routine medical practice. (RPIS 5278)

Research Medicine and Radiation Biophysics Division

464. Development of Radionuclides for Medical Imaging Purposes

T.F. Budinger

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\$250,000

The objectives of this research are to develop methods for the incorporation of short-lived radionuclides into biochemical substrates and to utilize these radiolabeled compounds in studies of human physiology. The distribution of these substrates can be followed noninvasively using positron emission tomography (PET) and single-photon emission computed tomography (SPECT) imaging techniques. Radiolabeled biochemicals can be designed to follow similar in vivo pathways as naturally occurring compounds; their use permits the investigation of physiological processes in normal and diseased states.

These researchers are investigating the use of both radioscope generators and short-lived cyclotron-produced radionuclides for incorporation into radiopharmaceuticals. Each class of radionuclide has its own chemical and practical advantages and disadvantages. Radioactive metal ions eluted from generators pose difficult chemical problems associated with their incorporation into useful radiopharmaceuticals. Lipophilic complexes containing ^{68}Ga , ^{82}Rb , and ^{113}Sb remain to be fully exploited for blood flow measurements and other in vivo applications, while ^{123}I and ^{62}Cu have recently been incorporated into blood flow pharmaceuticals. In contrast, short-lived cyclotron-produced radionuclides such as ^{18}F , ^{15}O , and ^{11}C have been incorporated into a wide variety of radiopharmaceuticals. The chemical nature of these atoms is quite different from the metal ions eluted from generators, and their application is virtually unlimited. However, these short-lived radionuclides require an onsite cyclotron. Thus, the researchers continue to investigate both generator- and cyclotron-produced radionuclides to enable critical comparison of their properties and development of those radiopharmaceutical agents for which each radionuclide is best suited.

To date, the researchers have developed a reliable ^{82}Rb generator for myocardial blood flow and blood-brain barrier permeability studies, an ^{123}I generator for brain and heart blood flow studies, and ^{68}Ga -labeled platelet, porphyrins, and lipoproteins to study cardiovascular disease. The researchers have produced ^{18}F - and ^{11}C -radiolabeled hypoxic cell markers, receptor ligands, glucose analogues, amino acids, fatty acids, and ^{15}O -water for PET studies of physiologic function in brain, heart, and tumor tissue. (RPIS 0330)

465. Human Brain and Heart Metabolism and Flow Measurements by Noninvasive Techniques

T.F. Budinger

R.H. Huesman

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\$950,000

The objective of this program is to develop and use new technologies for the study of atherosclerosis, heart disease, aging, mental disorders, and radiation effects. This project

focuses on advanced emission tomography and nuclear magnetic resonance (NMR) systems that are beyond currently envisioned commercial implementation. The joint approach of new technologies and experimental physiology is applied to medical science problems using a team of physicists and research physicians devoted to the development of quantitative methods of experimental medical science. In addition to the noninvasive methods of nuclear medicine and NMR, autoradiography, tracer studies in vitro, and, most recently, synchrotron light source studies of elemental changes are used. The program has a major emphasis on mathematical modeling and statistical analyses. These instrument development programs offer, as an integral part, the technological transfer in collaboration with private industry.

Early results of this work included the first demonstration of the clinical usefulness of the Anger camera and the tomoscanner. More recently, researchers of this program developed quantitative reconstruction algorithms, new compartment modeling methods, the statistical basis of dynamic positron emission tomography (PET), clinical studies of a unique 2.6 mm resolution PET instrument, and tritium NMR studies of carbohydrate metabolism.

Planned work includes medical science studies of dementia, schizophrenia, heart disease, tumor metabolism, and response to therapies using the researchers' unique high resolution PET and high field NMR. In addition, advanced mathematical techniques will be used to continue the development of algorithms for reconstruction of multidimensional image distributions and to enhance the quantitative aspects of medical science data analysis. (RPIS 0331)

466. Improved Instrumentation for Positron Tomography

S.E. Derenzo

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\$200,000

The objective of this project is the development of advanced detector concepts for the imaging of positron-labeled tracers in humans and animals with substantial improvements in spatial and temporal resolution. The researchers' tomograph design approach is to encircle the patient with multiple rings of detectors having a good detection efficiency, good spatial resolution, and low dead time. In addition, this design rejects multiple crystal interactions, measures depth of interaction to correct for parallax, and uses many parallel high speed circuits for high maximum event rates.

The researchers' first task is to develop advanced detector systems for multilayer, ultra-high resolution positron emission tomography (PET) using a combination of scintillating crystals, photomultiplier tubes, and position-sensitive solid state photo-detectors with miniaturized electronics.

The second task is to develop new scintillators for PET by (1) systematically searching heavy atom compounds to find those exhibiting fast fluorescence, (2) measuring the scintillation properties of optical crystals of promising compounds, and (3) investigating scintillation mechanisms through the use of synchrotron radiation.

The third task is to use the ultra-high resolution Donner 600 Crystal Tomograph to investigate (1) adaptive optimal reconstruction filters, based on the number of events and distribution tracer and (2) the effect of accepting multiple-crystal events on sensitivity and resolution. New techniques developed in this work will permit these researchers and others to build improved positron tomographs for the benefit of medical research throughout the world. (RPIS 2420)

467. Vascular and Blood Diseases

S.N. Ebbe

(415) 486-5435

\$120,000

A goal of this project is to identify early and advanced vascular lesions in animals by their interaction with radioisotopically labeled substances. Recent work has focused on the distribution of labeled platelets, red cells, albumin, and indium oxine in the tissues of mice during the first few days after irradiation (1050R, ^{60}Co). Kidneys, livers, spleens, and lungs were tested. Of these only the kidneys showed an abnormality in the irradiated mice. ^{111}In -oxine, administered as such or as labeled platelets, accumulated in the kidneys in excess of amounts found in unirradiated controls; red cells and albumin did not. The specificity of the findings for the kidneys makes them important because late renal effects of radiation may be lethal. This mouse model may offer the possibility of detecting and modifying the early effects that may, in turn, modify the late renal effects. Experiments are continuing.

Abnormalities of platelets, megakaryocytes, leukocytes, and lipids were found when rabbits with Watanabe heritable hyperlipidemia (WHHL) were tested to determine if hematological abnormalities would accompany the known deficiency of receptors for low density lipoprotein (LDL). The findings were compared with earlier results in rabbits with dietary hypercholesterolemia. The differences observed by researchers have caused them to suggest that LDL receptors and/or the uptake of triglycerides by megakaryocytes affect proliferation of megakaryocyte progenitors and fragmentation of megakaryocytes into platelets. Additional animal models with specific lipid abnormalities are being studied.

Interactions between megakaryocytes and their micro-environment have been evaluated in cultures of isolated megakaryocytes. Researchers now plan to determine the effects of extracellular matrix proteins on the production and growth of megakaryocytes in longer term, stroma-dependent cultures of normal murine bone marrow and marrow from Sl/Sl^0 mice. (RPIS 0328)

468. Effects of Heavy Particle Radiation

J.I. Fabrikant

(415) 486-6188

\$130,000

The objectives of this research are to investigate the physical and biophysical properties of heavy ions and their application and to follow cellular and metabolic events in the mammalian brain following irradiation, including regulatory control, cell proliferation kinetics, regional cerebral blood flow (rCBF)

dynamics, and reaction of the brain to radiation injury. Heavy ions are used as neuroscience probes to investigate cell and tissue injury and repair and dose, dose-rate, and time-dependent responses for induction of central nervous system damage.

Researchers are currently examining the physics of beam delivery, dose localization, dose distribution at BEVATRON; analysis of subependymal brain cell proliferation and differentiation; myelin maintenance; pathobiology of brain response to focal heavy ion (He, C, NE) beams; NMR and PET scanning of mammalian brain and in selected research protocol patients.

Future research will (1) investigate physical properties of heavy ion beams at BEVATRON; (2) examine beam quality and RBE/LET relationships for protons, He, C, and Ne ions and photons; (3) follow cellular and metabolic events of heavy ion radiation injury and repair; (4) observe the dynamics of brain cell proliferation and differentiation, including nucleic acid metabolism, processes of myelination, and homeostasis; (5) examine the pathophysiology, rCBF dynamics and altered metabolism in irradiated human brain using NMR and PET scanning; (6) apply charged particles for stereotactic radiosurgery of intracranial vascular and neoplastic disorders in humans; (7) develop applications for heavy charged-particle research and technology transfer for radiation protection, radiation oncology, and radiosurgery treatment procedures for humans, as appropriate. (RPIS 0329)

469. Heavy Ion Radiosurgery

J.I. Fabrikant
(415) 486-5435

\$284,000

The objectives of this research are to: (1) perfect stereotactic heavy charged particle Bragg peak radiosurgery at the BEVATRON for treatment of intracranial vascular disorders and brain tumors in humans; (2) examine pathophysiologic mechanisms of cerebrovascular reaction to charged particle radiation injury in brain; (3) apply nuclear medicine procedures to study pathophysiological and metabolic events in brain following heavy ion radiation; (4) investigate physical properties and beam quality of heavy ions for developing beam delivery systems for medical applications; (5) establish relating biological effectiveness (RBE) and linear energy transfer (LET) and dose-effect relationships for different sites in the human brain; and (6) develop therapeutic strategies for clinical application through technology transfer to community hospital-based facilities. The rationale behind this approach is that heavy ion beams have superior physical and biologic properties in brain over protons and photons; their advantages include improved dose distribution in Bragg peak, sharp lateral and distal borders, less scattering and range straggling for same range in tissue, minimal dose beyond the target volume, and improved peak-plateau RBE ratios. The experimental approach involves a stereotactic neuroradiologic procedure to determine size, shape, and location of intracranial targets. Charged particle treatment planning and dosimetry and precise patient immobilization are used to deliver optimal dose locations and dose distributions. Nuclear medicine procedures such as nuclear magnetic resonance (NMR) and positron emission tomography (PET Xe-CT) allow researchers to examine pathological and normal

tissue reaction to radiation injury. Currently, more than 450 research patients (including 55 children) with intracranial vascular disorders have received treatment and follow-up; 80-85 percent were cured. NMR and PET studies have been correlated in 22 selected patients; comparisons of different radiation types and irradiation geometries have been made. The significance of this research is apparent: heavy ion radiosurgery obliterates selected intracranial vascular disorders, protects against brain hemorrhage, and destroys small brain tumors. Future research will (1) improve procedures with heavy charged particles at BEVATRON; (2) investigate helium-ion beams for greater precision (three-dimensional conformal treatment planning) and efficacy of radio surgery (treatment of very large AVMs, effects of fractionation) with reduced brain morbidity; (3) study pathophysiologic brain tissue reaction to injury, altered regional cerebral blood flow dynamics, and tissue metabolism following heavy ion irradiation and (4) study the means of technology transfer to community hospital-based programs, e.g., proton beam cancer therapy. (RPIS 0332)

Los Alamos National Laboratory

Los Alamos, NM 87545

Isotopes and Nuclear Chemistry Division

470. Imaging Agents for Lymph Nodes and Inflammatory Lesions

D.A. Cole
(505) 667-0832

\$305,000

The goal of this project is to develop methods for using a radio-labeled porphyrin ($^{67}\text{CuTCPP}$) to diagnose and treat lymphatic and other cancers that spread to the lymph nodes. To successfully accomplish this goal, a complete understanding of the biological, physiological, and kinetic properties of $^{67}\text{CuTCPP}$ must be understood. To accomplish this, this project is examining the physiological mechanisms and radiopharmacokinetic properties associated with the localization of $^{67}\text{CuTCPP}$ in lymphatic and other cancers in the lymph system. (Clinical testing of the radiolabeled porphyrin will then constitute the second phase of this research and thus is several years away.) Results of the researcher's examination show that $^{67}\text{CuTCPP}$ has a high affinity for lymphatic cells and other cancers such as lung cancer, and that $^{67}\text{CuTCPP}$ has a high affinity for inflamed lymph nodes. These results demonstrate that the uptake of $^{67}\text{CuTCPP}$ in inflamed lymph nodes is 4 times greater than that in surrounding muscle and 8 times greater than that in fat. Kinetic studies show that the uptake of $^{67}\text{CuTCPP}$ in inflamed lymph nodes occurs in two phases and that this uptake is proportional to the degree of inflammation. This finding suggests that $^{67}\text{CuTCPP}$ may be useful in identifying inflamed lymph nodes before other visible signs, such as increased lymph node size or the presence of cancer (lymphoma) cells in the lymph node, can be detected by other procedures. Future radiopharmacokinetic and mechanistic studies will investigate the uptake of $^{67}\text{CuTCPP}$ in lymph nodes with lymphatic and other cancer types. (RPIS 4989)

471. Detection and Treatment of Lung Cancer Using $^{67}\text{CuTCPP}$

D.A. Cole

(505) 667-0832

\$200,000

As a result of exposure to high levels of radon and its daughters, uranium miners experience a very high incidence of lung cancer. This fact has been documented especially at St. Mary's Hospital, Grand Junction, Colorado, where a study of uranium miners of the Colorado Plateau has continued for more than 30 years. In a collaborative research effort, Los Alamos National Laboratory and St. Mary's Hospital are investigating methods to detect and treat lung cancer in uranium miners with a new radiolabeled porphyrin, 5, 10, 15, 20-tetrakis (4-carboxyphenyl) porphinate (TCPP). (This porphyrin can be easily radiolabeled with the radioisotope ^{67}Cu ; $^{67}\text{CuTCPP}$.) Preliminary results of this study demonstrate that the uptake of TCPP in lung tumor cells is greater than other commonly used porphyrins, such as hematoporphyrin. To date, 14 miners have been evaluated with TCPP. In all cases, the concentration of TCPP in the lung cancer sputum cells of miners with the disease has been many times greater than in miners without lung cancer. Based on these positive results, the goal of this research is to develop $^{67}\text{CuTCPP}$ into a radiopharmaceutical that can be used to treat uranium miners and other lung cancer patients. To accomplish this goal, determinations are being made regarding: (1) the localization and therapeutic characteristics of $^{67}\text{CuTCPP}$ in lung tumors and (2) the biological and physiological properties of $^{67}\text{CuTCPP}$ in living systems. This critical information is being ascertained using tissue culture and animal tumor models. (RPIS 5211)

472. Complementary Positron Emission Tomography and Therapeutic Radiopharmaceuticals

E.J. Peterson

K.C. Ott

(505) 667-1237

\$300,000

This research develops radiopharmaceuticals using elements that have isotopes suitable for positron emission tomography (PET) and therapeutic applications. In these cases, the identical labeling chemistry applies to the complementary isotopes of the same element. This research develops radiopharmaceuticals of exceptional in vivo stability incorporating these complementary isotopes. These agents are then applied to radiopharmaceutical applications such as labeling of biomolecules (peptides, proteins, antibodies) and radiosynthesis of receptor ligands. The strategies are particularly applicable to the isotope pairs $^{64,67}\text{Cu}$ and $^{72,76}\text{As}$. This research takes advantage of the new $^{72}\text{Se}/^{72}\text{As}$ generator developed at Los Alamos National Laboratory (LANL), and the fact that ^{72}As is a positron emitter suitable for the development for PET radiopharmaceuticals. This generator could have a greater impact on PET than the $^{82}\text{Sr}/^{82}\text{Rb}$ generator has had due to the highly developed chemistry of arsenic as compared to that of rubidium. The specific aims of this research are to (1) design and synthesize different agents, (2) test their stability, (3) develop methods of synthesis under radiolabeling conditions, and (4) determine the

effect that the labeling chemistry has on the biomolecule activity. This research takes advantage of several radioisotopes uniquely available at LANL. (RPIS 5212)

473. Medical Radioisotope Research Program

E.J. Peterson

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\$617,000

The program strives to maintain a balance between (1) production of radioisotopes of demonstrated or potential value in medicine and biomedical research and (2) research concentrating on new radioisotopes and biomedical generators, radiopharmaceutical development in labeling, and in vivo animal studies, to demonstrate the utility of new agents discovered in this program. The Medical Radioisotopes Research program, referred to as the Core program, is the major vehicle for support of research activities described in (2) above. Production activities described in (1) are pursued in a companion program supported by DOE's Office of Nuclear Energy. A balanced effort between production and research ensures the continued vitality of both activities. The research directed at new isotope development involves conceptualization of an isotope and applications, development of the targeting and irradiation schedules to maximize isotope yields, investigation of the separations chemistry required to isolate and purify the isotope of interest, and experiments to explore applications. The biomedical generator development contributes to the availability of short-lived research radionuclides, positron emission tomography agents, and therapeutic radioisotopes. Labeling efforts focus on radiolabeling monoclonal antibodies for tumor imaging and internal radiation therapy, with initial focus on ^{67}Cu as the radionuclide and porphyrins as the chelating agents for coupling to antibodies. (RPIS 1160)

Physical Life Sciences Division

474. Imaging Function in the Human Brain

E.R. Flynn

C.C. Wood

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\$420,000

These researchers are developing technology to augment the noninvasive imaging of function of the human brain in three dimensions with high spatial and temporal resolution for clinical and neuroscience application. The approach is to use the technology of magnetoencephalography (MEG) to measure the external magnetic fields produced by neuronal electrical activity within the brain. This technique has the potential to localize neuronal generators to a spatial accuracy of a few millimeters and temporal accuracy of a few milliseconds. Los Alamos National Laboratory (LANL) currently operates several MEG systems using specially designed shielded rooms and data acquisition systems. Clinical trials of MEG in a variety of applications are under way at the Veterans Administration Hospital in Albuquerque, New Mexico, in collaboration with LANL; basic neuroscience experiments are carried out at LANL.

This program's goal is to develop the capability for rapid three-dimensional images of brain function following sensory stimuli or cognitive tasks. To accomplish this, novel sensor arrays using superconducting image plane surfaces are being developed, which result in large arrays that are self-shielding, more sensitive, and less expensive. Advanced concepts in reconstruction of neural sources from MEG data in combination with magnetic resonance imaging and other information are also implemented. These concepts are combined with innovative theories of magnetic field generation from electrical sources within the brain, new methods of imaging three-dimensional functional maps of the brain, and advanced techniques for localizing sensors and reducing errors of measurement. (RPIS 4823)

Theoretical Division

475. Modeling of Cochlear Mechanisms

G. Zweig

(505) 667-8496

\$31,000

Cochlear implants are being developed to give a class of profoundly deaf people the sensation of sound and, it is hoped, the ability to understand speech. The implants contain a set of electrodes that electrically stimulate the nerve fibers that leave the cochlea and travel to the brain. Ideally, the electrodes should be driven by a filtered output of a simulation of the human ear. The goal of this research is the simulation of the human ear. The long-term goal is to use filtered output of that simulation to excite the electrodes of cochlear implants. Knowledge gained from the simulation may also be used to improve the performance of more conventional hearing aids by electronically preprocessing sounds to make them more intelligible. This work is also providing a theoretical basis for setting standards to limit the exposure of humans to noise. The initial phase outlines a program for simulating the nonlinear mechanics of the cochlea. (RPIS 5618)

Oak Ridge Institute for Science and Education

Oak Ridge, TN 37831

Medical Sciences Division

476. Radiopharmaceutical Internal Dose Information Center

E.E. Watson

(615) 574-3448

\$260,000

The Radiopharmaceutical Internal Dose Information Center (RIDIC) is a continuing program that contributes to nuclear medicine research by providing radiation dose estimates as requested. The staff compiles biological data from research facilities and from published literature, develops physiological models, analyzes data, and calculates radiation dose estimates. The center works to improve dose estimation by developing

new models and techniques. The center's bibliographic database now contains more than 35,000 entries on references relating to dose calculation. In May 1991, RIDIC conducted the fifth in its series of international symposia on radiopharmaceutical dosimetry, particularly as related to radiolabeled immunoconjugates and other therapeutic agents. Also in FY 1991, RIDIC broadened its scope to include dose estimates for occupational exposures. By January 1992, the center will publish the proceedings from the symposium to provide a resource for dosimetrists and others who need this information. The center hopes to become a repository of biological data for dose estimation. The center encourages nuclear medicine centers to collect appropriate data during controlled trials as well as routine practice. (RPIS 1932)

Oak Ridge National Laboratory

Oak Ridge, TN 37831

Biology Division

477. Monoclonal Antibodies for Study of Metastases

S.J. Kennel

(615) 576-0212

\$475,000

The goal of this task is to understand the expression of cell surface molecules on tumor cells and use mouse model systems to optimize accumulation of radiolabeled monoclonal antibodies (MoAb) at tumor sites. MoAb to the beta-4 subunit of integrins, a class of cell adhesion molecules, are used to probe the expression and function of this integrin in vivo. The beta-4 subunit is unique in that it has a very large cytoplasmic domain of unknown function and it is overexpressed in many murine and human carcinomas. Specific protein quantitation and messenger ribonucleic acid and genomic DNA analyses with cloned cDNA probes should better define the role of this integrin in metastases. These anti-integrin MoAb and others with target sites inside blood vessels provide tools to test basic principles of biodistribution and catabolism of MoAb. Some of these MoAb have potential for diagnosis of metastases by external body scanning or for adjuvant therapy through directed drug delivery. (RPIS 5003)

Health and Safety Research Division**478. Nuclear Medicine and Biomedical Radioisotope Technology**

F.F. Knapp, Jr.
K.R. Ambrose
A.P. Callahan
D.W. McPherson
S. Mirzadeh
P.C. Srivastava
 (615) 574-6223

\$750,000

This program supports DOE's role in promoting beneficial applications of nuclear technology. Its primary purposes are the design, development, and testing of radiopharmaceuticals with diagnostic and therapeutic applications in nuclear medicine. Design, synthesis, characterization, and biological testing of radiopharmaceuticals in laboratory animals are major areas of endeavor. Principal areas of interest include development of new radiolabeling techniques and of new agents with applications in cardiology, neurology, and oncology. This program advances biomedical applications of nuclear technology, especially development of improved radiopharmaceuticals for use in nuclear medicine procedures involving the early detection, diagnosis, and therapy of pathologic conditions. Fulfillment of these goals is realized through medical cooperative programs in which new research products are supplied to collaborators for further preclinical evaluation and development of clinical feasibility. (RPIS 1161)

479. Biomedical Radioisotope Technology Development

F.F. Knapp, Jr.
A.P. Callahan
S. Mirzadeh
 (615) 574-6225

\$345,000

This research supports the development of radioisotope research, processing technology, and radionuclide generator systems to provide the technology required to make available radionuclides of biomedical interest. The principal focus is the evaluation of radiochemistry and radioanalytical methods to provide radionuclides of high specific activity and radiochemical and chemical purity. Processing technology involves the development and optimization of chemical processes to obtain radionuclide products of sufficient purity for biomedical applications. The goals are to develop the technology required to provide radionuclides for medical research using state-of-the-art technology. Collaboration with medical cooperative programs provides opportunities for further preclinical and clinical evaluation with extramural programs. This program complements the Nuclear Medicine and Biomedical Radioisotope Technology Program, which is directed toward the design, development, and biological testing of new tissue-specific radiopharmaceuticals. (RPIS 3765)

480. Radiolabeled Nucleoside Probes for Tumor Diagnosis

P.C. Srivastava
 (615) 574-6223

\$154,000

This project involves conducting exploratory research to promote medical applications of nuclear technology. The study is developing new techniques for the synthesis and radiolabeling of nucleosides and related compounds for in vitro and in vivo evaluations. The goals of the project encompass the design and development of structurally modified nucleosides, preparation of new analogues radiolabeled with radionuclides, and their evaluation in tumor-bearing animals. The objective of this study is to identify nucleosides with cytotoxic properties, high tumor uptake, and specificity through collaborative arrangements with medical cooperatives. The results of these studies will indicate feasibility of these new agents for potential clinical diagnosis of and therapy for cancer. A further application is the coupling of cytotoxic nucleosides with tumor-specific antibodies for delivery to the tumor site to improve selectivity for tumor diagnosis and therapy. (RPIS 5037)

Biotechnology: Medical Applications

Offsite Grants

University of Alabama
 Birmingham, AL 35294

Center for Nuclear Imaging Research**481. Consortium to Develop Medical Uses of Nuclear Magnetic Resonance Imaging**

G.M. Pohost
 (205) 934-5266

\$95,000

The Center for Nuclear Imaging Research, University of Alabama at Birmingham and the Biomedical Imaging Center, University of Tennessee at Knoxville established a partnership in 1987 to expand their unique capabilities in developing and disseminating new nuclear imaging technologies. These two multidisciplinary institutions share complementary strengths in basic biomedical science as well as a history of regional leadership in research and education.

The overall objective of this project is to develop a consortium to utilize the strengths of two institutions with established excellence in nuclear imaging science. The goal is to optimize the development of new techniques in and uses for nuclear magnetic resonance imaging and positron emission tomography to improve understanding of pathophysiology and to improve diagnosis and therapy of human disease states. (RPIS 10637)

ALEM Associates

Boston, MA 02115

482. Improved Scintillator Materials for Medical Applications

A. Lempicki

(617) 236-1025

\$50,000

Cesium fluoride (CeF_3) has potential advantages as a scintillator for positron emission tomography (PET) scanning. It has almost the same density as currently used bismuth germanate (BGO), but is at least 10 times faster. The main problem with using the fluoride is its lower light output, approximately half that of BGO. Detailed spectroscopic work shows that CeF_3 should be capable of improved efficiency because CeF_3 emission is, to some degree, nonradiatively quenched. The main objective of this program is to find the reason for this quench and eliminate it. CeF_3 would then clearly become superior to BGO. The Phase I project is attempting to demonstrate this improvement by growing a series of compositions of $\text{La}_x\text{Ce}_{1-x}\text{F}_3$ in order to identify the impurity or defect responsible for the quench. The project is being carried out in cooperation with Optovac, Inc.

Improved efficiency in CeF_3 will make the material a prime candidate for large scale use in medical applications such as PET scanning. This fluoride, operating at a tenfold increase in speed, would replace BGO. PET cameras utilize large numbers of crystals (more than 1,000) producing a potentially major market. (SBIR)

Boron Biologicals, Inc.

Raleigh, NC 27606

483. Inexpensive Pathways for the Synthesis of Boronophenylalanine and New Boron-Containing Agents

B.F. Spielvogel

(919) 832-2044

\$500,000 (2-year funding)

Boron neutron capture therapy (BNCT) has a clear theoretical advantage over other techniques as a method of delivering cell-killing radiation to tumors. Boronophenylalanine (BPA) is currently being investigated in the U.S. for BNCT where it has Food and Drug Administration approval as an investigational new drug. Clinical trials are to begin soon. BPA has been used clinically in Japan for BNCT treatment of melanoma and is also under intensive investigation elsewhere, most notably in Europe and Australia. To obtain therapeutically useful concentrations of boron (specifically, the neutron-capturing B-10 isotope), large quantities of BPA are needed. Current processes for preparing L- ^{10}BPA (the B-10 enriched form desired for BNCT) consist of many steps and not only are labor intensive, but produce a very low yield of B-10 enriched product, resulting in high product cost. In Phase I, it was demonstrated that BPA can be prepared in a one-pot synthesis from readily available compounds. Phase II is concerned with optimization of this process and/or related ones to develop

and scale up the most cost-effective commercial preparation. Applying the synthetic methodology developed in Phase I and being refined in Phase II, other related boronated amino acids will be prepared and evaluated for the efficacy as BNCT agents.

Low cost synthesis of B-10 enriched L-BPA is the major result of this research. The availability of this material at a reasonable cost should permit clinical trials using BPA for BNCT to proceed in a rapid and cost-effective manner. The synthetic methodology developed may also be applied to the synthesis of related compounds of high commercial value. (SBIR)

484. New Boron-Containing Amino Acids and Peptides for Boron Neutron Capture Therapy

B.F. Spielvogel

(919) 832-2044

\$500,000 (2-year funding)

Boron neutron capture therapy (BNCT) has a clear theoretical advantage over other techniques as a method of delivering cell-killing radiation to tumors. New boron compounds are needed that can selectively localize in tumors and, upon capture of thermal or epithermal neutrons, produce radiation that kills tumor cells but spares normal tissue and blood. The Phase I effort confirmed the premise that certain boron analogues of aromatic amino acids and/or their peptide derivatives, in cell culture studies, produce strong cellular retention and concentration. The retention is maintained even after cell washing. The results strongly suggest the potential for significant improvement relative to compounds now available and proposed for clinical trials. For example, some compounds in this latter category do not bind and show only transient cellular concentration. The Phase II effort is preparing a variety of specific boron-containing aromatic amino acids and their di- and higher peptides, for study of their structure-activity relationships for BNCT. B-10 enriched derivatives and peptides with higher boron content will be prepared. In vivo experiments are being carried out to determine compounds of the highest efficacy. In addition, because many of the boronated amino acids and peptides have shown antitumor activity, pharmacological studies of new compounds are also being carried out.

The project should result in new boronated amino acids and peptides possessing chemotherapeutic activity and also designed for BNCT for the treatment of cancer. The new compounds may also be expected to have other potentially valuable biological and pharmacological (e.g., hypolipidemic and anti-inflammatory) activity. (SBIR)

485. New Gadolinium-Boron Compounds for Neutron Capture Therapy

B.F. Spielvogel

(919) 832-2044

\$49,986

Neutron capture therapy is a very promising therapy for certain tumors, such as gliomas and melanomas. Several nuclei have high cross sections for thermal neutrons, of which boron-10 (^{10}B) and gadolinium-157 (^{157}Gd) have been shown to be very promising. ^{10}B has a high cross section for thermal neutrons and

a very versatile chemistry. ^{157}Gd has the highest cross section for thermal neutrons and, being paramagnetic, is good for magnetic resonance imaging. A combination of these two nuclei in a single entity should provide a single, more convenient way to diagnose and treat tumors. Phase I research focuses on the synthesis of a molecule containing both ^{10}B and ^{157}Gd and on evaluating its stability, toxicity (LD_{50}), and in vitro efficacy. Phase II research will be concerned with the evaluation of in vivo efficacy, structure-activity relationship studies to optimize efficacy and determine the pharmacokinetics, tissue distribution, and toxicity (safety) of lead compound(s).

Successful completion of Phase I and Phase II should provide one or more new boron-containing gadolinium complexes that can be successfully used for magnetic resonance imaging of tumor tissue followed by tumor destruction by neutron capture. (SBIR)

486. Novel Base Boronated Oligonucleotides for Boron Neutron Capture Therapy

B.F. Spielvogel

(919) 832-2044

\$499,885 (2-year funding)

Boron neutron capture therapy (BNCT) has a clear theoretical advantage over other techniques as a method of delivering cell killing radiation to tumors. BNCT effectiveness would be greatest if the boron targeted the cell nucleus, and lower concentrations could be used. Phase I established the feasibility of preparing two types of protected and (base) boronated nucleotide "monomers" for chemically synthesizing oligonucleotides. These monomers are of the phosphoramidite and H-phosphonate class. A decamer was synthesized using a boronated nucleotide phosphoramidite. Model studies were also carried out on the boronation of presynthesized oligonucleotides. Phase I clearly showed that boronated oligonucleotides could be designed to operate in an "antisense" capacity, i.e., directly targeting unique portions of the genetic code, affecting only a specific gene. Phase II assesses the potential of designing tumor seeking, nuclease resistant, boronated antisense nucleic acids. These acids can potentially (1) target specific defined genetic material by the antisense mechanism to slow or stop gene expression (tumor seeking agents may be attached to the boronated antisense agents), (2) cause maximum BNCT cell kill by reason of association with genetic material, and (3) cause a chemotherapeutic effect due to the amine-substituted boranes. A coordinated multidisciplinary approach is being used in which the synthetic efforts will be combined with and guided by pharmacological studies (tumor tissue cytotoxicity screens, in vivo studies, mode of action, and acute toxicity), physicochemical studies (stability and base pairing studies of boronated nucleotides and oligonucleotides with normal nucleotides and oligonucleotides), and biological efficacy studies using the boron neutron capture reaction. Invaluable fundamental information is being obtained not only for use in BNCT, but also for investigating the promising area of antisense technology for many disease states (including cancer, viral, parasitic) and applications in agriculture.

Novel boronated oligonucleotides that target the nuclear material of tumor cells for maximal cell kill by BNCT should result. These boronated oligonucleotides should show considerable other antitumor activity as well as antiviral, antiparasitic, etc. (SBIR)

Boston University

Boston, MA 02215

Chemistry Department

487. Scintillation Materials for Medical Applications

A. Lempicki

(617) 353-9581

\$127,000

This project is evaluating different Ce doped scintillation materials for detectors in medical applications. Emphasis is on basic physical processes involved in the effect of scintillation to formulate basic criteria, which can be used to evaluate the final physical limitations on the performance of different Ce materials. Comparison between theoretical and practical achievement parameters is useful for evaluation of potential capabilities of a given material. The parameters of highest concern are energy efficiency (light output) and speed. (RPIS 10295)

University of California, Davis

Sacramento, CA 95816

Department of Internal Medicine and Radiology

488. Copper-67 Lym-1 Feasibility Trial of Therapy for Lymphoma

S.J. DeNardo

(916) 734-3787

\$634,000

Substantial regression of B cell lymphoma and leukemia has already been demonstrated using Lym-1 monoclonal antibody (MoAb) labeled with I-131. Complete remissions were achieved. Those obtained at higher radiation dose rates have generally been more prolonged, with some at 1-2 years at present.

Success in treating B cell malignancies with I-131 labeled Lym-1 is being extended by a major effort in therapy with Cu-67 Lym-1, which has been pioneered by the DOE program. Recent pharmacokinetics and early therapeutic responses with this radiopharmaceutical substantiate previous projections that Cu-67 Lym-1 could offer a therapeutic advantage in treating lymphoma over I-131 Lym 1. Y-90 labeled DOTA will be studied along with In-111 DOTA Lym-1 to determine further modifications needed in the present chemistry to produce an effective therapeutic radiopharmaceutical. Lymphomas and related diseases represent special cases for radioimmunotherapy because of their documented radiosensitivity and immunodeficiency; they thus offer a unique opportunity to conduct these therapeutic feasibility studies in a responsive human model.

Using murine and chimeric L-6 and other MoAbs to treat breast cancer, the strategies developed in taking Lym-1 antibody from the bench to the patient are being applied. A number of MoAbs for treatment of breast cancer have been examined. L-6 was chosen for prototype studies because of its characteristics and because adequate amounts of murine and chimeric L-6 were available. Additional reasons for selecting L-6 were its similarity to Lym-1 in that it has cytotoxicity in vitro. After pharmacokinetic studies with I-131, Ch L-6 therapy studies in five patients revealed clinical response in four of them. Several other promising MoAbs, including one that internalizes into the cell, are being investigated because of their potential and because they offer additional therapeutic or mechanistic opportunities. Breast cancer is different from B cell malignancies because immunodeficiencies are less likely, the tumor is less radiosensitive, and antigen targets are generally less homogeneous. This allows exploration of differences and similarities. Breast cancer is more common than B cell malignancies but shares with B cell malignancies no current hope of curative therapy after initial metastasis.

The chemistry of attachment of conjugates to antibodies and their impact on immunological targeting and biological activities (cytotoxicity), metabolic fate, and therapeutic index continue to be a major strength and function of this program. From the beginning, this grant has supported the conception, synthesis, and development of the first macrocyclic bifunctional chelating agent TETA (6-p-nitrobenzyl-1, 4, 8, 11-tetraazatetradecane-N,N',N'',N'''-tetraacetic acid and its derivatives, including Lym-1-2IT-BAT) for use in Cu-67-based radioimmunodiagnosis and therapy. This work has led to the further development of several new macrocyclic bifunctional chelating agents for copper and other metals.

Using specific, biologically active, radiolabeled MoAbs (such as Lym-1, L-6, and CH L-6), the influence of factors such as amount of administered MoAb; amount of and schedule for administered radionuclide; radiation dose rate; alterations to tumor delivery by use of internalizing MoAbs; and variations in the characteristics of the radionuclide, chelate, linkage, and site-specific attachments for radionuclides will continue to be studied. Methods to be used include those developed in the last 3-5 years in this DOE program; quantitative imaging that provides absolute amounts (and concentrations) of MoAb in tumor and organs for pharmacokinetics and radiation dosimetry in patients; tomographic imaging estimates of tumor volume; and in vitro tests for in vivo cytotoxicity. Statistical and protocol designs that supply the most information from the fewest patients are being used. (RPIS 9900)

University of California, Davis Medical Center

Davis, CA 95616

Department of Nuclear Medicine

489. Testing the Validity of a Receptor Kinetic Model via TcNGA Functional Imaging of Liver Transplant Recipients

R.C. Stadalnik

(916) 453-3684

\$108,000

Hepatic binding protein (HBP) is a hepatocyte-specific receptor for serum asialoglycoproteins. The receptor also recognizes a synthetic glycoprotein that has been developed as a radiopharmaceutical (^{99m}Tc)-galactosyl-neoglycoalbumin (TcNGA). This research describes the correlation between receptor parameters measured in vivo modeling of TcNGA and those measured by in vitro radioassay of biopsied liver tissue. Eleven patients with diffuse hepatic disease went through percutaneous liver biopsy followed by a TcNGA functional imaging study. In vivo measurements of HBP quantity R_0 and forward binding rate constant k_0 obtained from the kinetic analysis of TcNGA liver and blood time-activity data were compared to total receptor quantity and the HBP-TcNGA association constant K_A as measured by Scatchard binding assay of the biopsied tissue. The correlation coefficients between in vivo and in vitro measurements were 0.73 (df=8, $p=0.015$) and 0.98 (df=8, $p<0.01$) for R_0 and k_0 , respectively. The in vivo measurements of HBP biochemistry via kinetic analysis of the radiopharmaceutical time-activity data reflect the average concentration and affinity of the receptor. This study further substantiates the validity of TcNGA as a quantitative probe for the HBP receptor. (RPIS 9709)

University of California, Irvine

Irvine, CA 92715

Beckman Laser Institute and Medical Clinic

490. A Center for Excellence for the Medical Application of Lasers

M.W. Berns

(714) 856-6996

\$492,000

This research is developing a university hospital-based center of excellence for laser medical research and application. This is a multidisciplinary program that cuts across basic science and clinical boundaries. The ultimate objective is to translate basic scientific and technical knowledge into new therapeutic and diagnostic modalities. This would be accomplished in a combined setting of a regional teaching hospital and its major outpatient laser surgicenter and research facility. The aim of this program is technology development and application as opposed to the already existing strong programs in basic science and biophysics. (RPIS 10548)

**University of California, Los Angeles
Laboratory for Biomedical and
Environmental Sciences
Los Angeles, CA 90024**

Division of Nuclear Medicine

**491. Nuclear Medicine Applications: Chemistry/
Biochemistry**

J.R. Barrio

(310) 825-4167

\$401,000

The chemistry/biochemistry nuclear medicine program focuses on the use of cutting-edge chemistry and biotechnology to design and develop drugs (biological imaging probes) targeting very specific regulatory processes that are either implicated or known as the bases of diseases. These processes are also studied in vivo using imaging techniques (confocal fluorescence microscopy, autoradiography, and positron emission tomography) for which modern concepts in structural chemistry, imaging, and pharmacology have merged to establish a new discipline of biological imaging.

In biological imaging, a concept in which a biological probe traces a specific biochemical process in a predictable manner for in vivo use was developed. To be effective, the radiolabeled biological probe should be specific for the process to be evaluated (i.e., a neurotransmitter synthesis) and should have only limited metabolism.

The objectives and requirements for designing an imaging probe of specific biological processes are identical to those required for drug design. For this research, these two concepts have merged to form the basis of a new discipline and a new vision of medicine. Researchers have thus targeted several problems on the rational biochemical design of site-directed analogues or drugs (i.e., for aromatic amino acid decarboxylase), vesicular transport models (i.e., dopamine-D₂ receptors). Drug and probe design is thus rationally made by interaction with physicochemical experimental data obtained in vivo and pharmacokinetic information. A newly begun drug and image probe development program focuses on the fundamental biology by which cells communicate and function through processes such as genetic message transcription, cell signal transduction, second messengers, and protein translation.

Using these tools, researchers are studying brain chemistry in health and disease (i.e., Parkinson's disease, depression) and the effects of drugs of abuse (i.e., cocaine, amphetamines). (RPIS 9233(A))

**492. Nuclear Medicine Applications: Molecular and
Cellular Biology**

D.C. Chugani

(310) 825-9600

\$577,000

The emphasis of this work is on the development and use of model systems to study basic issues, raised as a result of in vivo human positron emission tomography studies, at the cellular and molecular level. These model systems include (1) immortal

rat neural cell lines developed for the study of nervous system development and regulation of neurotransmission as well as for evaluation of neural transplantation to correct degenerative diseases of the brain and (2) the culture of human brain tissue obtained from patients treated surgically for the control of seizures. Immortal neural cell lines have been established from embryonic rat brain using ts58A, a retroviral vector containing the oncogene temperature-sensitive large T antigen. Transformed cells that have been established divide at 33° C. At 39° C, the cells stop dividing, and in the presence of appropriate growth factors, the cell lines differentiate into cells with neuronal properties. The immortalized cell lines were established using cells from the mesencephalon, the brain region containing dopamine-producing cells, and the striatum, one of the target tissues for these cells; researchers were interested in the regulation of dopamine synthesis and release and in the regulation of dopamine receptors in neurodegenerative diseases, such as Parkinson's disease. In addition to these rat cell lines, cultures have been established from human cortex of patients with hemimegalencephaly who underwent hemidecortication for the control of seizures. Approaches similar to those used for the rat cells are being used to induce these human cell lines to differentiate. Both human and rat neural cell lines are important tools for the study of normal and abnormal brain development and function.

In another area of research, the function of a vault ribonucleoprotein particle that was recently discovered is being studied. Researchers have shown the lines of evidence that indicate that this particle plays a key role in the translation (movement) of messenger RNA from the nucleus to the cytoplasm to provide the means for the synthesis of proteins from the genetic code. (RPIS 9233(B))

493. Nuclear Medicine Applications: Physical Sciences

E.J. Hoffman

(310) 825-8851

\$369,000

The physics and instrumentation research program investigates the physical and methodological aspects of applying radiation measurement technology to nuclear medicine imaging techniques, particularly positron emission tomography (PET). Researchers are developing new instruments and better methods of employing current instrumentation. Basic instrumentation development is conducted in the physical sciences laboratory on the benchtop, with components of imaging systems such as detectors and associated electronics. PET techniques are developed in clinical or animal PET imaging laboratories by characterizing performances of fully assembled PET systems, modifying hardware or software to compensate for deficiencies, and developing data acquisition and processing techniques to obtain the best possible measurement and image quality from the data.

Ongoing projects are as follows.

(1) One project is the application of a new fully three-dimensional image reconstruction technique to total body PET scans. The patient bed is stepped through the PET system to

image the whole body. Because the full body length is being imaged, only a short time is allowed at one position, and the increased sensitivity of the three-dimensional technique is vital to the success of the total body imaging. Once a diagnosis of cancer is made, it is vital to determine whether the cancer has spread as metastases. PET total body scans appear to be very sensitive to metastases, and the technique is uniquely able to determine whether radiation or chemotherapy is effective.

(2) New detector technology is being used to develop an intraoperative imaging probe. This device is to be used in the surgical removal of tumors, which are labeled by radio-pharmaceuticals (beta or gamma emitters) by injection before surgery. In surgery, the obvious tumor is removed, and the handheld probe images the surgical field to locate residual activity in difficult-to-locate residual tumor. Particularly in neurosurgery, it is difficult to locate the edges of the tumor, and it can be equally damaging to remove too little tumor or too much healthy tissue.

(3) To improve image quality, an ongoing collaboration uses a new mathematical technique maximum likelihood to reconstruct PET image data. In a study in which artificial lesions were added to image data from normal volunteers, detectability of known lesions was significantly higher with the maximum likelihood method. Effectively, the technique increases sensitivity without extra cost in hardware or extra dose to the patient. (RPIS 9233(C))

494. Nuclear Medicine Applications: Biomathematics

H. S.-C. Huang
(310) 825-6647

\$369,000

The general goal of research in the Biomathematics Section is to help through the use of new mathematical computer and engineering techniques the evaluation of new tracers or drugs in their development and to improve the usefulness of positron emission tomography (PET) and other nuclear medicine imaging techniques for early diagnosis and treatment of various diseases. New nuclear medicine imaging techniques (e.g., PET) allow noninvasive assessment of local tissue biological function in humans. However, these new techniques require sophisticated mathematical processing of the measurements ranging from tomographic image reconstruction, image processing, and tracer kinetic modeling to statistical estimation. Application and development of novel mathematical techniques play an important role in the continuing improvement of these techniques. Projects active in the Biomathematics Section include (1) the modeling of the kinetics of a tracer called FDOPA for studying the central dopaminergic nerve system and for understanding the pharmacokinetics of L-dopa, a drug commonly used for treating Parkinson's disease; (2) the modeling of cardiac tracers (e.g., N-13 ammonia and C-11 acetate) for their use in assessing tissue function and viability of myocardium in patients with coronary artery disease for cardiomyopathies; (3) the development of techniques (e.g., image registration and maximum likelihood image reconstruction) to minimize noise and errors in various data collection and processing steps; and (4) the

development of new mathematical estimation techniques to maximize the reliability of the information extracted from dynamic studies.

The interdisciplinary nature of the projects dictates that research is performed in close collaboration with biologists, radiochemists, biochemists, physicians, and physicists. (RPIS 9233(D))

495. Nuclear Medicine Applications: Neuroscience

J.C. Mazzlotto
(310) 825-2699

\$699,000

Researchers are mapping the functional organization of the human brain in health and disease. There are two components to this research. First, normal individuals performing a wide variety of behavioral tasks are examined to probe the systems that allow for vision, movement, hearing, language, memory, and thinking. Using positron emission tomography and magnetic resonance imaging, researchers have subjects perform a wide variety of tasks while measuring cerebral physiology and biochemistry. These measurements depict the parts of the brain active during performance of the task. In addition, by using the same techniques to follow subjects as they become proficient in learning a task, researchers can observe the change in these networks and systems that reflect the actual learning process. Appropriate technology and data analysis approaches are being developed to acquire, interpret, and display the vast amounts of data collected in these studies. Collaborations with laboratories in Canada, Europe, Asia, and throughout the United States have led to the establishment of consortia to distribute the tasks and the acquisition of data among many centers, thereby expanding and expediting everyone's efforts.

The second phase involves the study of disorders of the brain, including the evaluation of patients with stroke (cerebral infarction), brain tumors, and degenerative diseases of the brain such as Alzheimer's, Parkinson's, and Huntington's disease. By serially evaluating patients with these disorders, researchers have identified and plotted the natural history of the biological alterations of these diseases. This previously unavailable information is a critical prelude to providing objective tests for evaluating experimental therapies. Already these methods have been used to serially observe changes in brain biochemistry that result from the implantation of tissue in the brains of patients with Parkinson's disease and to compare the growth of this tissue with the clinical state of the patient. Results have been confirmed and replicated by laboratories worldwide. Currently, the ability to activate the brain is being combined with these disease states to better clarify how the brain adjusts to disease, reorganizes, and maintains function in the face of injury. These latter issues are important in designing experimental therapies and rational approaches to neurorehabilitation. (RPIS 9233(E))

496. Nuclear Medicine Applications: Cyclotron*N. Satyamurthy**(310) 825-6231***\$485,000**

The focus of this research is to develop an integrated and simplified technology for the production and delivery of radiopharmaceuticals for positron emission tomography (PET). The major areas of endeavor are accelerators for the production of radioisotopes, automated radiochemical synthesizers, and the integration of these two technologies into a single system.

The radioactive labels of greatest value in PET are the positron-emitting radioisotopes of carbon (C-11), nitrogen (N-13), oxygen (O-15), and fluorine (F-18). The lifetimes of these isotopes are so short (half-lives between 2 and 110 minutes) that a PET facility necessarily requires an onsite production capability. Even a state-of-the-art PET program, which utilizes the most modern cyclotron for radioisotope production, suffers from the complex and very expensive nature of the accelerator. The ultimate success and wide acceptance of PET in a clinical environment largely depends on the miniaturization and cost-effectiveness of the radioisotope production.

The radiofrequency quadrupole (RFQ) linear accelerator system, a revolutionary technology developed during the past few years, holds the greatest promise in this regard. Such a system would be compact, lightweight, and easy to operate and would greatly reduce installation and operating costs. A collaborative effort towards the development of a super-conduction RFQ accelerator is currently underway.

The advancement of the principles and technology of automated chemical synthesizers for the production of positron-labeled compounds is based on developing unit chemical operations in a standardized instrument approach. A particular rational drug designed by the Chemistry Section can be synthesized by a preprogrammed sequence of operations controlled by a personal computer. These systems are similar to the DNA biosynthesizer and benefit from DNA sequencer technology developed recently by biotechnology firms.

The union of the compact and miniaturized accelerator with the fully automated chemical synthesizer into a single system will increase the efficiency and cost-effectiveness of the radiopharmaceutical production. (RPIS 9233(F))

497. Nuclear Medicine Applications: Cardiovascular Sciences*H.R. Schelbert**(310) 825-3076***\$614,000**

The Cardiovascular Sciences Program seeks to develop novel techniques for probing the human heart's function and biochemical activity. Once validated, these new approaches are then applied to patients with cardiovascular disease. Current and past efforts have succeeded in uncovering biochemical hallmarks of reversibly dysfunctional myocardium. This accomplishment has significantly affected the diagnostic and therapeutic approach in patients with end-stage cardiac disease. Efforts to identify mechanisms that underlie these abnormal states of contractile function are also under way.

These efforts entail the establishment of animal experimental models so that alternating and associated histological and ultrastructural derangements can be characterized and understood in terms of fundamental abnormalities in substrate metabolism and its regulation. Equally important are future studies on the temporal evolution of these abnormalities, on the mechanisms of adaptation of contractile function and metabolism to chronic low flow situation, and on how these adaptive processes respond to therapeutic restoration of blood flow. Exploration of these changes in adaptive processes is also being examined at the level of genetic expression, employing molecular biology techniques. A second major aim is to characterize determinants of coronary vascular blood flow, which is now possible because of the development of reproducible noninvasive approaches for quantifying regional myocardial blood flow. These studies seek to characterize in addition to hemodynamic and mechanical determinants of blood flow modulatory effects of endothelial-derived substances, of substances affecting directly vascular smooth muscle, possibly gender-related differences in coronary vasomotor control as well as means by which these regulatory mechanisms can be altered by pharmacological interventions. (RPIS 9233(G))

**University of California, San Francisco
School of Pharmacy****San Francisco, CA 94143****Department of Pharmaceutical Chemistry****498. Carboranyl Amino Acids for Site-Specific Neutron Capture Therapy of Malignant Melanoma***S.B. Kahl**(415) 476-4684***\$34,000**

The development of third-generation compounds for site-specific delivery of boron to neoplastic cells is necessary for effective boron neutron capture therapy (BNCT) in the U.S. Among the most attractive third-generation compounds are those whose selective uptake is based on specific biochemical pathways known to be different in cancer cells than in normal cells. Malignant melanoma is an especially inviting target for BNCT, because aromatic amino acids are known to be actively transported and accumulated by melanoma cells as precursors for melanin biosynthesis. A rational biochemical mechanism thus exists for selective loading of boron in these tumors. This approach has been used clinically by Mishima and coworkers in the apparently successful treatment of three human melanoma patients, using L-paraboronophenylalanine, a phenylalanine derivative containing one boron atom per molecule.

This work synthesizes a variety of aromatic and pseudo-aromatic amino acids which contain the carborane moiety. This group delivers up to 10 boron atoms per molecule, is exceptionally stable and nontoxic, and can be manipulated successfully in a wide variety of organic reactions. Computer molecular modeling of the icosahedral cage shows that the cage is nearly bio isosteric with a phenyl ring and that

compounds in which the cage replaces a phenyl ring should be recognized by phenyl recognition sites in such biological systems as the aromatic amino acid uptake systems of melanin-producing cells. A new, higher yield synthesis of carboranylalanine, the carborane analogue of phenylalanine, has been developed at the University of California, San Francisco. Other methods of carboranylalanine synthesis are being explored, and new potential false precursors bearing the carborane cage for evaluation in BNCT radiochemotherapy of malignant melanoma are being synthesized. (RIPS 10103)

University of Chicago

Chicago, IL 60637

Department of Radiology

499. Instrumentation and Quantitative Methods of Evaluation

R.N. Beck

(312) 702-6270

\$757,000

This research aims to further the development of radiotracer methodology for quantitative studies of physiological processes in health and disease. This goal is being pursued through two closely related lines of research: (1) the development of new radiotracer materials for specific applications, conducted under a companion grant for radiopharmaceutical research and (2) the development of new imaging hardware and software for improving the quantitative determination of distributions of these radiotracer materials (both spatially and temporally) in animals and humans.

Research projects to improve imaging methods are organized into three sections.

(1) Imaging with gamma-ray emitters that address issues of collimation, attenuation, and scattering.

(2) Imaging with positron emitters that include implementing a new superresolution technique to improve the quality of positron emission tomography images. These research projects are attempting to extend the range of applications or radiotracer methods and improve the quality of images obtained in nuclear medicine. These projects are also addressing the special requirements imposed by the development of new radiopharmaceuticals and the specific studies of collimation, attenuation, and scattering as previously outlined.

(3) Methodology for quantitative evaluation of image quality. (RPIS 9487)

500. Quantitative Studies in Radiopharmaceutical Science

M. Cooper

(312) 702-6271

\$750,000

The principal objective of this project is to develop advanced methods to retrieve quantitative information concerning in vivo biological processes using radiotracers. Novel synthetic approaches are used to produce radiopharmaceuticals.

Mathematical models are applied to characterize biodistribution, localization, and rates of change, from tomographic images used to determine local tissue concentrations. Image analysis methodologies for three-dimensional visualization and quantitation are applied including expert-system approaches. In vivo animal and human studies are used to acquire experimental data and examine effects induced from pharmacological, physiological, and biopsychological challenges. Feasibility studies are conducted to examine pathophysiological changes and correlations of structural (computed tomography, magnetic resonance imaging) and functional (position emission tomography, single-photon emission computed tomography) imaging applied. Significant advances made in this work include new approaches to image correlation, development of new radiopharmaceuticals for studies of glutamate receptors, and novel studies on the effects of glucose and insulin on neuronal metabolism. An effect of alcohol on subject mood was correlated with regional brain metabolic changes. The range of metabolic brain change and regional effects from cognitive challenges and changes in awareness, including sleep, has been documented. This work is designed to reveal new knowledge of human pathophysiology, biochemistry, and behavior. (RPIS 9530)

501. Development of Gamma-Emitting, Receptor Binding Radiotracers for Imaging Brain and Pancreas

R.C. Reba

(312) 702-5968

\$255,000

The research objectives are to develop muscarinic acetylcholine receptor (m-AChR)-binding radiotracers, selective for m1-, m2-, and m3-AChR subtype in either the central nervous system (CNS) or in the peripheral cholinergic system, and to develop lipophilic, tertiary amine analogues of HC-3 that bind to the high affinity choline uptake system in the CNS for external imaging using single photon emission computed tomography or positron emission tomography. Dramatic reduction in the density of presynaptic muscarinic acetylcholine receptors (m2-subtype) and affinity choline uptake sites has been reported in the brains of Alzheimer's disease patients. (R,R)- and (R,S)-stereoisomers of 3-quinoclidinyl 4-iodoben-zilate (4IQNB), a potent m-AChR radiotracer that is nonselective for subtypes, have been developed. Detailed in vitro and in vivo studies of this compound labeled with (¹²³I or ¹²⁵I) have been published. A group of m1-selective AChR antagonists of lower lipophilicity than that of 4IQNB have been developed. On the basis of existing structure-activity relationships, the m2-selective AChR antagonist capable of crossing the blood-brain barrier has been designed and synthesized. Unlike any previously known m2-selective compounds, this compound can penetrate the blood-brain barrier. (RPIS 9830)

University of Cincinnati Cincinnati, OH 45221

Department of Chemistry

502. Development of More Efficacious Tc-99m Organ Imaging Agents

W.R. Heineman
(513) 556-9210

\$150,000

The long-range objective of this research is to develop more efficacious technetium-99m radiopharmaceuticals for use as imaging agents in diagnostic nuclear medicine. Analytical techniques are being developed that are capable of separating clinically used radiopharmaceutical mixtures into their component technetium complexes. Administration of the isolated, single most effective imaging complex, rather than a mixture of technetium containing complexes as is the current clinical practice, minimizes radiation exposure to the patient and maximizes diagnostic information available to the clinician. Analytical methods under development include (1) high performance liquid chromatography and capillary electrophoresis for the separation of diphosphonate radiopharmaceuticals into their components, (2) extended x-ray absorption fine structure spectroscopy and nuclear magnetic resonance spectroscopy for structural determination of imaging agents, and (3) electrochemical sensors for in vivo monitoring of imaging agents. (RPIS 9593)

Cornell University Ithaca, NY 14853

Baker Laboratory of Chemistry

503. Subcellular Distribution of Boron for Boron Neutron Capture Therapy Using Ion Microscopy

G.H. Morrison
(607) 255-3614

\$218,000

The application of the $^{10}\text{B}(\text{n},\text{d})^7\text{Li}$ reaction to boron neutron capture therapy (BNCT) for the treatment of brain tumors, malignant melanomas, and other cancers, has been very promising in recent years. However, some major technical issues have yet to be resolved so as to enhance BNCT clinical efficiency, such as the determination of intracellular boron concentration, localization, and tissue selectivity of boronated compounds. To serve these purposes, an ion microscopic method has been developed to quantitatively image boron—in both tissue cultures and sections—and to localize boron at the subcellular level. This project focuses mainly on tissue culture studies that are expected to provide a more fundamental understanding of BNCT. Research objectives are to (1) quantitatively determine cellular uptake of boronated compounds in pertinent cell lines and compare the uptake among different cell cultures and among different boronated compounds, (2) evaluate cell injury by means of K/Na ratio,

(3) determine the subcellular localization of boronated compounds using the imaging ability of the ion microscope, (4) investigate cellular Ca accumulation and influx during uptake and cell injury using the stable isotope ^{44}Ca as a tracer, (5) quantify boron distributions in tissue cryosections, and (6) establish strong collaborative ties to other research groups working on the many aspects of BNCT research.

Ion microscopy (IM) is an imaging technique based on secondary ion mass spectrometry. Samples are placed in a high vacuum and bombarded with a beam of energetic ions called primary ions. Generated by the impact of the primary ion beam from the top few atomic layers of the sample, the secondary ions are accelerated into a double-focusing mass spectrometer. After mass filtration, the secondary ions are projected onto an array detector so that their final positions correspond to their original positions on the sample surface. The final output of the instrument is thus a two-dimensional image showing the distribution of a specific element on the sample surface. Therefore, IM is capable of localizing any element or isotope in the specimen, with a sensitivity in the ppm range and a spatial resolution on the order of 0.5 μm , and has broad applications in biological, materials, and geological sciences. (RPIS 10440)

Duke University Medical Center Durham, NC 27710

Department of Radiology

504. Single-Photon Emission Computed Tomography Assay of Radiolabeled Monoclonal Antibodies

R.J. Jaszczak

(919) 684-2711

\$61,000

The accurate determination of the distribution of radiolabeled monoclonal antibodies (MoAbs) is important for calculating dosimetry and evaluating pharmacokinetic variables such as antibody dose and route of administration. A major long-term objective of this project is to determine the utility of single-photon emission computed tomography (SPECT) for quantifying the biodistribution of MoAbs labeled with the clinically relevant radionuclides iodine-123 (I-123) and indium-111 (In-111). This project aims to compare the effects of three methods of radiolabeling anticarcinoembryonic antigen (CEA-110): on the immunoreactivity and affinity of the antibody iodination by Iodogen, the tin-containing ester methods, and an indium chelate method. The biodistribution of anti-CEA labeled by the three methods is to be compared in tumor-bearing and normal mice. Subsequent studies of the pharmacokinetics of I-123 and In-111 labeled anti-CEA are to be determined by SPECT measurement. Pharmacokinetics is to be assessed with Monte Carlo simulations and by scanning phantoms containing I-123 or In-111 activity in regions of uniform and nonuniform attenuation. The ability of SPECT to quantitate I-123 and In-111 distributions is to be assessed, and new acquisition geometries and reconstruction algorithms for improved quantification are to be evaluated. (RPIS 10112)

505. Positron Emission Tomographic Imaging of Tumors Using Monoclonal Antibodies*M.R. Zalutsky*
(919) 684-2711

\$125,000

The project objective is to develop methods for using positron emission tomography to increase the diagnostic and therapeutic potential of radiolabeled monoclonal antibodies. Antibodies are to be labeled with Fluorine-18, Bromine-76 and Bromine-75 and evaluated in vitro and in vivo for tumor specificity. The pharmacokinetics of these labeled antibodies is to be evaluated in pet dogs with spontaneous tumors. The goal is to obtain more accurate dosimetry estimates for both tumor and normal tissues and to provide an approach for monitoring the response of tumors to therapy. (RPIS 10000)

Hypres, Inc.

Elmsford, NY 10523

506. Imaging Systems for Biomedical Applications*M. Radparvar*
(914) 592-1190

\$49,984

Many of the activities of the human body manifest themselves by the presence of a very weak magnetic field outside the body. This field is so weak that an ultrasensitive magnetic sensor is needed to allow specific biomagnetic measurements. Superconducting quantum interference devices (SQUIDs) are extremely sensitive detectors of magnetic flux and have been used extensively to detect the human magnetocardiogram and magnetoencephalogram and other biomagnetic signals. To utilize a SQUID as a magnetometer, the SQUID's transfer characteristics should be linearized. This linearization requires extensive peripheral electronics, thus limiting the number of SQUID magnetometer channels in a practical system. The projected digital SQUID would integrate the processing circuitry on the same cryogenic chip as the SQUID magnetometer and eliminate the sophisticated peripheral electronics. Such a system would be compact, cost effective, and require minimal support electronics. This project is leading to the development of thin-film digital magnetometer/gradiometer chips. In addition to having on-chip processing circuitry coupled to a SQUID, each chip will also have an integrated superconducting transformer to facilitate its interface to an external pick-up coil. This effort makes it possible to design and fabricate single chips that will contain arrays of digital SQUIDs for integration in a multichannel SQUID system, thereby reducing the cost and complexity of such systems. The Phase I project is concerned with the design, fabrication, and evaluation of digital SQUID chips.

This project should lead to the development of thin-film SQUID chips as ultrasensitive magnetometers. The chip is a self-contained magnetometer with on-chip processing circuits and requires minimal support electronics. Consequently, arrays of such chips could be very cost effective for integration in

multichannel SQUID magnetometer systems for use in noninvasive biomedical instruments such as multichannel magnetocardiograms and magnetoencephalograms. (SBIR)

University of Illinois

Urbana, IL 61801

Department of Chemistry**507. Fluorine-18-Labeled Androgens and Progestins: Imaging Agents for Tumors of Prostate and Breast***J.A. Katzenellenbogen*
(217) 333-6310

\$171,000

Many tumors of the breast and prostate contain receptors for progestins and androgens, respectively, and the presence and levels of these receptors can usually be correlated with the endocrine responsiveness of the cancer. These receptors also provide a potential mechanism whereby progestins or androgens, suitably labeled with gamma- or positron-emitting radionuclides, could be selectively concentrated to permit imaging of the tumor. Unlike the estrogen receptor, these receptors should still be useful targets for imaging in patients who are on estrogen or anti-estrogen hormonal therapy.

In this project, progestins and androgens are being prepared and labeled with the positron-emitting radionuclide fluorine-18. Ligands are being selected (1) to have very high affinity for the respective receptor, (2) to have low affinity for blood and nonspecific binders, and (3) to be reasonably resistant to metabolism. The progestins are derivatives of the potent progestins ORG2058 and promegestone R5020, norgestrel RU486, and the unusual retroprogestins; fluorine substitution is at ring or side-chain positions or attached through an ester linkage. The androgens are derivatives of the high affinity analogues mibolerone (R1881) or 2-oxa-metribolone; fluorine is being attached at the 16 β position or on a 7 α - or 17 α -methyl group. Fluorine incorporation reactions involve displacements on cyclic sulfates and trifluoromethanesulfonates. In vitro competitive binding studies are being performed on the unlabeled analogues to determine their binding characteristics, and uptake studies with the F-18 labeled progestins are being done in rats, using the uterus and DMBA-induced mammary tumors as targets. Uptake studies with the F-18 androgens are being done in castrate rats, using the ventral prostate and Dunning R3327 transplantable tumor as target sites. Ultimately, in collaborative studies, these radiopharmaceuticals are to be used with positron emission tomography to image the receptor-positive tumors. (RPIS 9468)

The Johns Hopkins University School of Medicine

Baltimore, MD 21205

Division of Nuclear Medicine

508. Synthesis of Tracers Using Automated Radiochemistry and Robotics

R.F. Dannals

(301) 955-2916

\$37,000

This research is developing a system for synthesis of tracers using automated radiochemistry and robotics (STARR), a fully automated approach for tracer synthesis. The research involves an integrated approach of radiochemistry modular laboratories and robotics to produce major high specific activity ^{11}C -radiotracers for use in positron emission tomography.

Specifically, the short range objectives of the research are to (1) automate ^{11}C -methyl iodide ($^{11}\text{CH}_3\text{I}$) production via an integrated approach using both radiochemistry modular laboratories and robotics; (2) demonstrate the automated capability utilizing the ^{11}C -methyl iodide in the synthesis of ^{11}C -methionine (a radiotracer that is useful even with a relatively low overall final specific activity, e.g., ~30 mCi/ μmole); (3) utilize ^{11}C -methyl iodide in the synthesis of 3-N- ^{11}C -methyl]piperone (a radiotracer that requires a moderately high overall final specific activity, e.g., ~300 mCi/ μmole); and (4) utilize ^{11}C -methyl iodide in the synthesis of [^{11}C]-carfentanil (a radiotracer that requires a relatively high overall final specific activity, e.g., ~3000 mCi/ μmole). (RPIS 10287)

Massachusetts General Hospital

Boston, MA 02114

Radiology Department

509. High Resolution Tomographic Instrument Development

G.L. Brownell

(617) 726-3805

\$331,000

This project is developing positron emission tomographic (PET) systems with maximum resolution for the desired application. These applications consist of imaging organs in the bodies and brains of humans and animals.

PCR-II (a cylindrical PET system) is in the final stages of development for imaging the human brain and body organs in children and in animals. The resolution will be 3 mm, and sensitivity will be adequate to support this resolution over a 24-cm-diameter source.

PCR-I, a single-ring PET system, will continue to be used for animal study, while PCR-II undergoes an intensive program of evaluation and optimization. Researchers will perform a variety of tasks.

(1) Complete the design and construction of PCR-II, an analogue-coded cylindrical positron tomograph. The design will use the principles proven by the performance of PCR-I, a single-ring analogue-coded system, and follow on from studies of two-dimensional coding currently under way using sectors of the cylindrical system. A Monte Carlo code will aid in the final design of the coding system and in the development of the data processing system.

(2) Further develop the three-dimensional algorithm now used for volumetric reconstruction of simulated sources. A reconstruction algorithm that will yield the maximum signal-to-noise ratio by balancing the marked increase in sensitivity with the corresponding increase in random and scatter coincidence rates is being developed.

(3) Demonstrate the performance of PCR-II in phantoms and, in collaboration with other investigators, animal models prior to clinical applications. Biological studies using PCR-I to image hearts, brains, and tumors in animals will continue until PCR-II is fully operational.

(4) Develop a positron microtomograph with submillimeter resolution for quantitative studies in small animals.

(5) Explore new techniques for detecting annihilation radiation, including new scintillators, new light detection systems, and new solid-state detectors. (RPIS 9642)

Wellman Laboratory of Photomedicine

510. Center of Excellence in Laser Medicine

J.A. Parrish

(617) 726-3995

\$350,000

This research is focusing on (1) the exploration and development of photosensitizers, (2) the development of new medical laser systems, and (3) the development of noninvasive optical diagnostic techniques. To this end, research fellowships have been established, biomedical research symposia are being organized, and research activities are being coordinated with a multidisciplinary matrix of academic, government, and industrial collaborators. The project will result in the establishment of a center to bring lasers and related technology from research to clinical practice and to transfer technology to the private sector. (RPIS 10555)

Massachusetts Institute of Technology

Boston, MA 02115

Department of Nuclear Engineering

511. Accelerator-Based Epithermal Neutron Capture Therapy: Design of Neutron Source and Irradiation Facility

J.C. Yanch

(617) 253-7017

\$63,000

An optimized design of an accelerator-based epithermal neutron beam for boron neutron capture therapy (BNCT) uses $\text{Li}(p,n)^7\text{Be}$ reaction with a 4mA, 2.5 MeV proton beam

generated by a Cascade Tandem accelerator. Neutrons emerge from the thick lithium target with energies ranging from 0 eV–800 keV and are subsequently altered by a moderator filter reflector shielding (MFRS) assembly. The design of this assembly has been carried out in two phases, using the three-dimensional state-of-the-art Monte Carlo code MCNP.

In Phase I of this design, MCNP was used to determine a usable range of energies for treatment of patients by BNCT. Simulating unidirectional, photon-free neutron beams of various diameters impinging on either cylindrical or elliptical brain-equivalent phantoms, the advantage depths (ADs) and advantage ratios (ARs) of a number of different mono-energetic neutron beams were determined. Assuming a ^{10}B tumor-to-healthy-tissue ratio of 30:3, neutrons of energies from 4 eV–40 keV were found to permit treatment to a depth of 7 cm in the brain, with an AR of at least 3. Maximizing the number of neutrons in this energy range pointed out choices for the materials and configuration of the MFRS assembly in Phase II.

Phase II involved using MCNP to investigate systematically the neutronic and photonic properties of various materials. By using this information, preliminary designs were simulated, and evaluated in terms of maximizing the therapeutic neutron flux (4 eV to 40 keV) emerging from the assembly. For the final design, AD and AR were maximized in brain-equivalent phantoms. Investigations of H_2O , D_2O , BeO , Al_2O_3 , and TiD_2 indicated that for the accelerator-produced neutrons, D_2O is the most efficient moderator, producing very few gammas and yielding a high quality neutron spectrum.

The accelerator neutron source with MFRS assembly as described above produces an epithermal neutron flux greater than $10^9 \text{ n/cm}^2\text{s}$. Brain tumor dose rates of 20 Gy in 100 minutes at AD of more than 7 cm are easily achievable. The design of the accelerator and target is proceeding on schedule. Some of the calculations may soon be confirmed, and biological testing may begin. (RPIS 10098)

Massachusetts Institute of Technology Cambridge, MA 02139

Harvard Medical School–MIT Division of Health Sciences and Technology

512. Short-Lived Radiopharmaceuticals

J.S. Adelstein
(617) 432-2184

\$500,000

The Harvard-Massachusetts Institute of Technology Research Program in Short-Lived Radiopharmaceuticals was established in 1977 to foster interaction among groups working at Harvard Medical School, the Massachusetts Institute of Technology, and Massachusetts General Hospital in fields related to radiopharmaceuticals chemistry. During this funding period, research is centering on the chemical basis of radiopharmaceutical action. The research has two principal themes: (1) the synthesis and use of neutral technetium and

rhodium complexes of high specific activity and (2) new approaches to the radiolabeling of immunoglobulins and their products and assessment of the biological consequences of various radiolabeling techniques. (RPIS 9547)

University of Michigan Medical Center

Ann Arbor, MI 48109

Division of Nuclear Medicine

513. New Techniques for Positron Emission Tomography in the Study of Human Neurological Disorders

D.E. Kuhl

(313) 936-5388

\$185,000

The objective of this project is to improve technical processes required for the future growth of positron emission tomography (PET) as a sophisticated research tool and for the transfer of this technology to clinical use. The focus is to develop more cost-effective and efficient means for producing new, functionally specific tracers and simpler, less expensive means for acquiring and interpreting quantitative data. Innovative radiosynthesis methods that have improved ^{11}C and ^{18}F synthetic processes have been introduced, and new objective analyses of the limitations and opportunities for quantifying regional PET data have been developed. Researchers expect to improve dramatically the speed and reliability of delivery of new PET tracers and provide means to improve knowledge of regional pharmacokinetics by extracting from PET data crucial information not being used with present methods. These DOE-supported studies are intended to improve the diagnosis and treatment of degenerative neurological diseases, mental illness, and brain tumors. (RPIS 9707)

514. Radiopharmaceuticals for Diagnosis and Treatment

D.E. Kuhl

(313) 936-5388

\$236,000

This project addresses the need in positron emission tomography (PET) for more simple and reliable synthetic procedures that should extend the research and clinical effectiveness of the method. A target for production of ^{18}F fluoride using an intermediate energy cyclotron was developed, fully tested, and brought into routine use. New synthetic routes to aryl ^{18}F fluorides, ^{18}F trifluoromethyl groups, ^{18}F fluorocatechois, and ^{18}F perfluoroalkyl ethers have been devised. The first applications of nucleophilic ^{18}F fluorination to synthesis of ^{18}F fluorothiophenes and ^{18}F fluoropyridazines have been reported. New fluorine-18 radiopharmaceuticals for the study of the dopamine reuptake system, GABA reuptake system, and calcium channels have been developed. One new radiopharmaceutical, ^{18}F GBR 12909 (dopamine reuptake inhibitor), has been brought into clinical trials for studies with PET. In the area of robotics, new applications of this technology in radiopharmaceutical metabolite analysis and preparation of a Zn-62/Cu-62 generator have been examined.

This work has expanded the field of fluorine-18 radiochemistry to several new classes of compounds (trifluoromethyl-substituted drugs, heterocycles, and perfluoroalkyl compounds), introduced several new radiopharmaceuticals to preclinical or clinical use, and shown that robotics can solve several radiation safety problems in the PET radiopharmaceutical laboratory. (RPIS 9794)

- 515. Noninvasive Evaluation of the Cardiac Autonomic Nervous System by Positron Emission Tomography**
M. Schwaiger
 (313) 936-5385 \$37,000

Positron emission tomography (PET) has been primarily applied to evaluate regional myocardial blood flow and myocardial substrate metabolism. With the introduction of tracers of the sympathetic and parasympathetic nervous system, the noninvasive evaluation of the autonomic nervous system and its relationship to other parameters of tissue function has become possible. Using the principles of tracer kinetic modeling, quantification of uptake and tracer distribution can be performed. This research concentrates on validating the new catecholamine analogue C-11 hydroxyephedrine in the animal model and in initial clinical studies. Developed at the University of Michigan, this compound is being used to quantify neuronal uptake and storage of catecholamines in the adrenergic nerve terminal. The specificity of this tracer is being tested, employing pharmacologic interventions that alter neuronal uptake and vesicular storage of norepinephrine. Initial clinical studies are defining the feasibility of the proposed quantitative PET approach in normal volunteers and patients with heart transplants (clinical model of cardiac denervation). Along with the evaluation of the sympathetic nervous system, a new tracer for the characterization of the parasympathetic nervous system is being investigated. The muscarinic receptor agent C-11 methyl-troponyl benzilate has been recently synthesized at the University of Michigan and has proven to bind specifically to peripheral muscarinic receptors in the rat model. Studies will evaluate the tracer kinetics of this new compound in the canine heart and relate its kinetics to the in vitro determination of muscarinic receptors. Again, pharmacologic blocking studies with receptor antagonists will be performed to define the nonspecific and specific binding of this tracer. The correlation of in vivo PET studies and in vitro receptor assays will determine how accurately this new PET approach estimates specific receptor binding in the heart. (RPIS 10382)

University of Missouri Columbia, MO 65211

Department of Chemistry

- 516. Bifunctional Chelates of Rh-105 and Au-199 as Potential Radiotherapeutic Agents**
E.O. Schlemper
 (314) 882-8374 \$63,000

The objective is to produce bifunctional chelates of the radionuclides Rh-105 and Au-199 which can be linked to antibodies. These antibodies will then localize in tumor tissue, and the radiation energy will destroy the tumor cells. The approach is to synthesize the bifunctional chelates, prove that they can be linked to the antibodies, and measure the biodistribution of the labeled antibodies in small animals. The final product is expected to be an improved method of cancer therapy. An extension of this objective is the use of the bifunctional ligands to complex other radionuclides of interest in nuclear medicine and applications other than labeled antibodies. (RPIS 9469)

Department of Radiology

- 517. Production of Radiolabeled Monoclonal Antibody Conjugates by Photoaffinity Labeling**
W.A. Volkert
 (314) 882-2557 \$30,000

The objective of this work is to synthesize ^{77}As - or $^{186}\text{Re}/^{188}\text{Re}$ -labeled photoaffinity labels (PALs) to be used to conjugate monoclonal antibodies (MoAbs) by photoactivation. New $^{186}\text{Re}/^{188}\text{Re}$ and $^{99\text{m}}\text{Tc}$ chelates that are stable have been synthesized and characterized at both tracer and carrier levels. The properties of these new chelates make them excellent candidates for eventual attachment to PALs. The synthetic route to produce ^{77}As -dithiol compounds has been developed, and the products of these compounds have been characterized. Several azido-based PALs have been examined, however, their quantum efficiency for linking to proteins is not sufficiently high for practical utility. Other PALs using different photoactivation moieties have been evaluated. The highest photolabeling yields of a PAL to proteins was 25 to 35 percent. This is not high enough to be used for routine photoconjugation of MoAbs, but is the highest yield yet reported, indicating that this approach continues to hold important potential for labeling MoAbs. (RPIS 10099)

The University of Nebraska Medical Center Omaha, NE 68198

Department of Radiology

518. Dosimetry & Quantitative Radionuclide Imaging in Radioimmunotherapy

P.K. Lechner

(402) 595-2739

\$217,000

Radioimmunotherapy (RIT) has resulted in partial and complete tumor remissions in some patients. To evaluate and optimize RIT, research is being carried out in quantitative imaging and the dosimetry of radiolabeled antibodies. Long-term objectives are to develop quantitative single-photon emission computed tomography (SPECT) imaging for tumors and normal tissues and computer algorithms and software for treatment planning in RIT. Specific aims are (1) developing better reconstruction algorithms for SPECT and improved methods for analyzing SPECT data (validation will be carried out in phantoms, beagle dogs, and tissue samples from patients); (2) developing improved methods for modeling biodistributions and extending betaparticle dosimetry to include uniform and nonuniform activity distributions and irregular shapes of tumors; (3) studying the effects of tumor heterogeneity, different types of antibodies, and radiolabels on radiation absorbed dose distributions; (4) testing the hypothesis that experimental data can be extrapolated to human tumors to optimize RIT. (RPIS 10499)

Ohio State University

Columbus, OH 43210

College of Pharmacy/Department of Pathology

519. Synthesis and Evaluation of Boron Compounds for Neutron Capture Therapy of Malignant Brain Tumors

A.H. Soloway

R.E. Barth

(614) 292-2509

\$216,000

Glioblastomas are one of the most lethal of all human cancers—even with aggressive treatment involving surgery, chemotherapy, and conventional radiation therapy, alone or in combination. A need to develop new methods exists for treating such tumors, which generally do not metastasize from the central nervous system (CNS). Boron neutron capture therapy (BNCT) is a binary chemoradiotherapeutic system that offers significant potential if high differential boron concentrations can be achieved between the glioma and its surrounding normal structures. The capture reaction from boron-10's absorption of thermal neutrons are high linear energy transfer alpha and lithium particles whose destructive effect will be confined to a radius of 10–14 microns. The overall objective of this research is to develop and evaluate boron compounds with high specificity for viable malignant gliomas.

The specific aims are to (1) synthesize boron analogues of glioma-active alkylating agents such as N-nitrosoureas and aziridinybenzoquinones; (2) synthesize lipophilic, boron-containing anticonvulsants and CNS depressants; (3) prepare carboranyl nucleosides with a potential for transformation into nucleotides within glioma cells; (4) synthesize carboranyl amino acids which through facilitated transport may penetrate the brain, thereby achieving elevated concentration in gliomas; (5) study the in vitro uptake and in vivo pharmacokinetics and tumor localizing properties of the above compounds in brain-tumor-bearing rats; (6) determine in vitro BNCT reactions of the most appropriate compounds in cell culture; and (7) assess the in vivo efficacy of BNCT with compounds having favorable in vitro tumoricidal activity and appropriate in vivo pharmacokinetics. (RPIS 10243)

Ohio State University Research Foundation Columbus, OH 43212

520. An Accelerator Neutron Source for Boron Neutron Capture Therapy

T.E. Blue

(614) 292-0629

\$199,000

A moderator assembly was designed, and calculations showed that an epithermal neutron source for the treatment of glioblastoma by boron neutron capture therapy (BNCT), is feasible for this moderator assembly and a 10 mA, 2.5 MeV proton beam. One objective of this project is to design and test a moderator assembly for a thermal neutron source for the treatment of superficial tumors by BNCT, using the Ohio State University Van de Graaff accelerator. The current of 2.5 MeV protons necessary to treat a patient in less than 1 hour is being identified. Another objective is to design and thermally test a target for a thermal and epithermal source of neutrons for BNCT. This target assembly is to be used with the moderator assemblies and must be able to dissipate 75 kW, the energy of a 30 mA, 2.5 MeV proton beam (75 kW is the design objective based on LAN 2 estimates of attainable proton currents, and the desire to reduce patient treatment time). The accomplishment of these two objectives, along with work previously completed, will result in the complete design of a target and moderator assembly neutron source for the treatment of both deep and superficial tumors by BNCT. (RPIS 10100)

University of Pennsylvania Philadelphia, PA 19104

Department of Radiology

521. Positron Ring System Using Angle-Type Detectors

J. Karp

(215) 662-7213

\$398,000

This project has four objectives. The first objective is to investigate the limits of a large, solid-angle positron emission tomography (PET) scanner using continuous position-sensitive detectors. This includes studying the tradeoff between improved sensitivity and increased scatter and random backgrounds. The second objective is to improve the performance of the NaI(Tl) position-sensitive detectors in terms of spatial resolution and count-rate capability. This includes extending the performance to the edge of the detector to minimize the gaps between adjacent detectors. The third objective is to develop a three-dimensional reconstruction algorithm applicable to the University of Pennsylvania PET (PENN-PET), as well as other volume-imaging scanners. This requires the algorithm to take account of the variation of the axial acceptance angle and to include normalization, scatter, and attenuation corrections. For the PENN-PET, the three-dimensional reconstruction algorithm must also compensate for the data missing in the gaps, although this may not be as significant in future designs with reduced gaps. The fourth objective is to carry over the concepts of improved scanner performance and volume imaging into the clinical research environment to assist in the work done with the PENN-PET scanners. Improved scatter, randoms, deadtime, and attenuation correction schemes will be implemented to improve the quantitative accuracy of the data. (RPIS 9797)

The Schepens Eye Research Institute Boston, MA 02114

Biomedical Physics Unit

522. Center of Excellence—Microlaser Microscope

R.H. Webb

(617) 742-3140

\$333,000

This project has two components: (1) development of an imaging system, made possible by the recent development of arrays of microlasers, which will lead to a novel confocal microscope, a solid-state, compact system with no moving parts; and (2) conduct of a group of laser-diagnostic and therapeutic efforts funded by other sources. The resultant miniature confocal microscope will combine the best features of both laser and disk scanner type and will open new fields, including in vivo confocal microscopy, as well as make an exquisite and inexpensive microscope widely available. Associated research projects are Laser Anomaloscope, Ti:Sapphire SLO, Spatially Resolved Refractometer, Corneal Shape Measurement,

Confocal Scanning Laser Microscope for Dermatology, Fiber Optic Ophthalmoscopic System, Scanning Laser Ophthalmoscope (SLO) Support, Multiplexed Laser Video Display for Evoked Potentials, Reading Aids, and Flow Cytometry. (RPIS 10557)

Science Research Laboratory Somerville, MA 02143

523. A New High Yield Cryogenic Target for Fluorine-18 Production

B.J. Hughey

(617) 547-1122

\$500,000 (2-year funding)

The objective of this project is to develop a new windowless cryogenic ice target for the reliable production of high yields of fluorine-18 (^{18}F), the most widely used radioisotope for positron emission tomography (PET). This target uses enriched ^{18}O -ice at liquid nitrogen temperature and has the capability of allowing operations at accelerator beam power loadings 20 times those allowed by the liquid ^{18}O -water targets currently in use. In addition, the cryogenic target uses only about one-tenth the enriched ^{18}O -water used by liquid targets. Development of the cryogenic target makes possible, for the first time (1) the production of very high yields (4 Ci or more) of ^{18}F with the medium energy PET cyclotrons presently in use in medical centers and government research laboratories in the U.S. and abroad; and (2) the production of high yields (1 Ci) of ^{18}F with the new economical, low energy accelerators for PET such as the Tandem Cascade Accelerator (TCA). Phase I demonstrated the technical feasibility of producing clinically significant quantities of ^{18}F in a cryogenic target. Greater than 80 percent of the ^{18}F produced in a prototype cryogenic target irradiated with the TCA proton beam was extracted in aqueous solution. The reactivity of the extracted ^{18}F was measured and found to be at least as high as the reactivity of ^{18}F extracted from conventional liquid water targets. In Phase II, the production of 1 Ci of ^{18}F in a TCA-irradiated cryogenic target and 4.6 Ci in a cyclotron target is demonstrated. Fully automated cryogenic targets designed specifically for clinical use are then fabricated and tested. The performance of the cryogenic target is being compared directly with a conventional liquid water target in tests at Washington University.

Several commercial benefits are expected to result from the introduction of the cryogenic ^{18}F target to the nuclear medicine industry. These include (1) improved cost effectiveness of supplying ^{18}F -pharmaceuticals; (2) improved target reliability, enhancing the ability of clinical PET centers to meet demanding patient schedules; (3) availability of very high ^{18}F yields, fostering the establishment of nuclear pharmacies; and (4) a significantly enhanced market potential for the new generation of economical, low energy accelerators. (SBIR)

Sloan-Kettering Institute for Cancer Research

New York, NY 10021

Department of Nuclear Medicine

524. Biomedical Research with Cyclotron-Produced Radionuclides

S.M. Larson

(212) 639-7373

\$450,000

This program uses basic nuclear medicine research methodologies to improve cancer diagnosis and treatment and to monitor treatment response based on cyclotron-produced radionuclides used as tracers for important biologic and pharmacologic processes. The program consists of three parts: (1) an innovative cyclotron radiochemistry and targeting project that will lead to the production of new positron-emitting radionuclides (I-124 and Ga-66), which are suitable for radiolabeling antibodies, as well as the radiolabeling of certain important drugs for later pharmacokinetic studies (including C-11 colchicine and C-11 methotrexate) and the radiolabeling by enzymatic methods of new metabolic tracers (particularly C-11 thymidine); (2) a novel method for monitoring multidrug resistance *in vivo* in human tumors, beginning with C-11 colchicine as a model compound; and (3) innovative radiochemistry and quantitative studies of positron-emitting radiolabels (I-124 and Ga-66) with potential for positron labeling of antitumor antibodies. This research emphasizes the imaging physics of quantitating of radionuclides such as I-124 as well as practical improvements in radiolabeling methodologies for certain antitumor antibodies (including 3F8, an antineuroblastoma antibody, and A-33, an anticolorrectal cancer antibody). (RPIS 9471)

Stanford University School of Medicine

Stanford, CA 94305

Department of Medicine

525. K-Edge Subtraction Angiography with Synchrotron X-Rays

E. Rubenstein

(415) 723-2883

\$250,000

The long-term objective of this research is to develop a transvenous synchrotron radiation-based x-ray optical system capable of providing clinically useful images of the coronary artery circulation. A dual beam, dual detector imaging system has been completed and used on human subjects. A medical beamline at the National Synchrotron Light Source (NSLS) has also been completed. The first human subject studies at NSLS were scheduled during October 1990. Progress has been very satisfactory. (RPIS 9647)

University of Tennessee

Memphis, TN 38163

Biomedical Engineering Department

526. Intravenous Coronary Angiography Utilizing K-Emission and Bremsstrahlung X Rays Produced by Electron Bombardment

H.D. Zeman

(901) 528-7099

\$30,000

This research studies the feasibility of developing an imaging system for coronary angiography using K-emission x rays produced by electron bombardment of metal foils rather than synchrotron x-ray sources. The source should prove less expensive and more practical for patient treatment than a synchrotron. Preliminary computer calculations indicate that the project is feasible with proper choice of electron energy, anode material, x-ray filters, and intravascular contrast agents. The research measures the x-ray spectrum, both K x rays and bremsstrahlung, produced by 3001,000 keV electron bombardment of rhenium and iridium foils. Signal-to-noise ratios are being studied with a water-filled human phantom and various soluble metal salts to simulate the absorbing and scattering properties of a patient. During subsequent work, the foil target heat dissipation problem at high electron current densities is being addressed. All the experimental work is taking place at Brookhaven National Laboratory, with the use of a laboratory accelerator and other facilities. The research will provide the physical data required to verify the theoretical calculations that a diagnostic quality image can be achieved. (RPIS 10707).

University of Tennessee

Knoxville, TN 37996

Biomedical Imaging Center

527. Consortium to Develop Medical Uses of Nuclear Magnetic Resonance Imaging

E. Buonocore

(615) 544-9663

\$95,000

The Center for Nuclear Imaging Research, University of Alabama at Birmingham and the Biomedical Imaging Center, University of Tennessee at Knoxville are seeking to establish a collaborative effort to enhance the development of nuclear imaging technology in the biomedical fields of nuclear magnetic resonance imaging and positron emission tomography. Through this consortium, the following tasks will be accomplished: (1) strengthening institutions by creating collaborative research projects oriented toward both basic science questions and the development of clinical applications and (2) establishing a program to train M.D. and Ph.D. candidates in nuclear imaging technologies. Although this work will not include large clinical research protocols, a

database for evaluation and dissemination of up-to-date clinical information regarding new nuclear imaging technologies will be established. (RPIS 10636)

University of Tennessee Medical Center Knoxville, TN 37920

Radiology Department

- 528. Boron in Nuclear Medicine: New Synthetic Approaches to Positron Emission Tomography and Single-Photon Emission Tomography Agents**
G.W. Kabalka
(615) 544-9670 \$169,000

The syntheses of site-specific, isotopically labeled compounds have become increasingly important in nuclear medicine due to recent advances in positron emission tomography (PET) and single-photon emission tomography. The complexity of the prerequisite physiologically active molecules puts restrictions on the synthetic approaches that can be successfully utilized. The limitations are particularly severe in PET, where many of the most useful nuclides possess very short half-lives.

The primary focus of this program has been to develop new methods for incorporating short-lived isotopes into agents used for measuring dynamic processes in vivo (steroids, esters, amines, etc.). The new methods often involve the use of boron compounds because these compounds have been shown to be excellent precursors to radiolabeled materials. Researchers developed an exciting oxygen-15 labeled alcohol that is being used in clinical trials involving in vivo blood pool measurements. They also developed a new method for stabilizing radiiodine towards in vivo deiodination by attaching the iodine to a vinyl group; the new iodovinyl technology is being utilized by a large number of medical research teams. Pioneering advances have been made in the attachment of these boron reagents to solid inorganic surfaces that generate solid-state, reactive substrates adaptable to automated radiopharmaceutical synthesis modules.

During the second phase of this project, researchers will be developing new organoborane transformations utilizing stable, solid-state organic and inorganic reagents for rapidly incorporating short-lived, medically useful isotopes such as nitrogen-13, oxygen-15, fluorine-18, an iodine-123 into physiologically active agents for use in nuclear medicine procedures. Polystyrene, polysaccharides, and mineral-based reagents are among the many exciting possibilities. Researchers will be attaching organoborane precursors to these agents to increase the efficiency of both the synthetic and purification methodologies. The targeted radiopharmaceuticals include agents for visualizing the myocardium, brain, uterus, and prostate. (RPIS 9525)

University of Texas **M.D. Anderson Cancer Center** Houston, TX 77030

Laser Biology Research Laboratory

- 529. Diagnostic and Therapeutic Applications of Diode Lasers and Solid-State Lasers in Medicine**
S.L. Jacques
(713) 792-3662 \$300,000

The project develops diagnostic and therapeutic uses of solid-state and diode lasers in medicine. The three diagnostic objectives are as follows: (1) reflectance spectroscopy via optical fibers to be developed for neonatal care and to include measurement of hyperbilirubinemia, monitoring of intravenous lines to detect needle extravasation, and assessing total body fluid volume; (2) fluorescence spectroscopy to be developed for diagnosis of cervical precancer and dysplasia, examination of the atherosclerotic process, and localization of precancer and cancer sites during clinical endoscopy; and (3) absorption and Raman spectroscopy to be applied to cervical diagnosis and atherosclerotic process.

The five therapeutic objectives are as follows: (1) photocoagulation therapy to be applied to prostate photocoagulation to treat benign prostate hyperplasia, and cyclophotocoagulation of ciliary bodies to treat glaucoma; (2) laser welding of cut blood vessels to be developed as a surgical tool; (3) cardiac laser studies to include laser angioplasty of atherosclerotic vessels and laser-induced acoustic waves to elicit relaxation of vascular spasm; (4) treatment of pigmented lesions by pulsed lasers to be studied, specifying the laser operating parameters that disrupt melanosomes; and (5) photodynamic therapy (PDT) studies that will employ solid-state lasers and diode lasers to achieve killing of tumors in small animals. A diode laser (690-nm wavelength) system for PDT will be developed. (RPIS 10552)

Texas A&M University College Station, TX 77843

Department of Nuclear Engineering

- 530. Considerations of Beta and Electron Transport in Internal Dose Calculations**
W.E. Bolch
J.W. Poston
(409) 845-4175 \$96,000

The research is using two Monte Carlo electron transport codes, EGS4 and OREC, to perform dosimetric studies at the molecular level, cellular, and suborgan level, and at the organ and whole-body level. The research is divided into five tasks. Task I continues current studies into the chemical mechanisms of damage to simple DNA molecules by free radicals produced within electron tracks. Work performed in Task II uses Monte Carlo

techniques to characterize distributions of absorbed dose within small volumes within organs. Task III continues the development of a mathematical phantom for use in the internal dose estimation. The phantom will have two primary features: (1) it will be composed of differential volumes for use in establishing intraorgan iodose contours, and (2) it will be based on realistic anatomical features derived from computer tomography and magnetic resonance imaging patient images. Tasks IV and V initiate research into improved mathematical models of and dosimetric calculations for the human brain and bone. This work will result in new estimates of absorbed doses within the various regions of the brain and the different structures of the bone such as trabeculae and bone marrow. (RIPS 9881)

Thomas Jefferson University
Philadelphia, PA 19107

Department of Radiation Oncology and Nuclear Medicine

531. Evaluation of Biological Response Modifiers in the Enhancement of Tumor Uptake of Tc-99m Monoclonal Antibodies

M.L. Thakur
(215) 955-7874

\$266,000

Imaging tumors with Tc-99m agents has several advantages over anatomical imaging with computerized tomography or magnetic resonance. Imaging tumors with radiopharmaceuticals continues to be challenging. Tc-99m monoclonal antibodies are promising agents, but, for the better delineation of primary tumors and metastatic lesions, enhanced uptake is required. Preliminary data have shown that, with the use of certain biological response modifiers (BRMs), tumor uptake was augmented by as much as 200 percent. To enhance this uptake even further, researchers want to optimize the quantities of three BRMs, determine the best route of their administration, and decide the most effective time of imaging. The work is being performed in nude mice bearing experimentally implanted human melanoma and colorectal carcinoma as well as two tumor-specific antibodies. Two other nonspecific agents are also being evaluated. (RPIS 10731)

Tufts-New England Medical Center
Boston, MA 02111

Department of Therapeutic Radiology

532. A Clinical Trial of Neutron Capture Therapy for Brain Tumors

R.G. Zamenhof
O.K. Harling
(617) 956-6171

\$225,000

Tufts-New England Medical Center/Massachusetts Institute of Technology has the necessary elements to initiate a clinical trial of neutron capture therapy (NCT) for the treatment of glioblastoma

multiforme and malignant melanoma. MITR-II has a good thermal neutron beam and a good epithermal neutron beam. These beams have been carefully characterized by state-of-the-art experimental dosimetry and Monte Carlo simulation. Clinical treatment planning methods are in place to ensure accurate and safe dose delivery to patients. A sensitive prompt gamma boron-10 analysis facility for quantitating boron-10 concentrations in blood and other tissues prior to patient irradiation has been developed along with a high resolution alpha track autoradiographic capability for examining boron-10 distributions in frozen tissue sections at the subcellular level. Promising studies are being conducted on the feasibility of using secondary ion microscopy to image the boron-10 distribution in tissue at very high resolution (down to approximately 1 micron) and sensitivity (down to less than 1 ppm), using a state-of-the-art secondary ion microscopy facility at MIT. New England Medical Center is supporting a clinical trial of NCT in its radiation oncology, neurosurgery, pathology, medical oncology, neuroradiology, and medical-physics services. (RPIS 9706)

University of Washington Cancer Center
Seattle, WA 98195

Department of Medicine

533. Improved Radioimmunotherapy of Hematologic Malignancies

O.W. Press
(206) 548-4938

\$106,000

The objective of this research is to improve the radioimmunodetection and radioimmunotherapy of cancer by enhancing retention of radiolabeled monoclonal antibodies (RABs) by tumor cell targets. Biochemical, morphologic, electrophoretic, chromatographic, autoradiographic, cytochemical, and analytic subcellular fractionation techniques are being employed to study the internalization, intracellular routing, and metabolic degradation of ¹³¹I-RABs by human leukemia and lymphoma cells obtained from patients on clinical trials. Five promising new approaches are being investigated to augment specific retention of RABs: (1) selection of slowly internalized and degraded RABs; (2) administration of pharmacologic agents that retard delivery of RABs to lysosomes or inhibit lysosomal enzymes; (3) adoption of novel tyramine cellobiose and para-iodobenzoyl radioiodination techniques that resist intracellular metabolism; (4) substitution of alternate radionuclides (e.g., ⁹⁰Yttrium or ¹⁸⁶Rhenium) for ¹³¹Iodine, since the former radioisotopes are retained intracellularly even after RAB catabolism; and (5) targeting novel new tumor antigens such as the HER2/Neu oncogene on breast and ovarian tumors. (RPIS 10708)

Washington University School of Medicine
St. Louis, MO 63110

Edward Mallinckrodt Institute of Radiology

534. Labeling of Receptor Ligands and Other Compounds with Halogen Radionuclides

M.J. Welch

(314) 362-8435

\$183,000

This project focuses on five major areas: (1) to continue studies on the usefulness of fluorine-18-labeled 16-fluoroestradiol-17 (¹⁸FES) for detecting estrogen receptor containing tumors and metastases and to attempt to correlate the uptake of the radio-labeled estrogen with the receptor levels; (2) to develop new labeling techniques for synthesizing halogen-labeled radiopharmaceuticals in high yield (of particular importance is synthesis of fluorine-18-labeled estrogens designed for reduced or directed metabolism); (3) to test the new fluorine-18-labeled estrogens, using an *in vivo* rat model; (4) to investigate the synthesis of and biologically evaluate fluorine-18-labeled ligands for the androgen and progesterone receptors; and (5) to apply robotics for synthesizing potentially useful compounds. Patient studies have been carried out with an estrogen-receptor-based ligand. This work has shown that the uptake of ¹⁸FES correlates well with receptor levels measured *in vivo* and that the uptake of the tracer is blocked in humans by the administration of the anti-estrogen tamoxifen. New ligands for the progesterone, androgen, and glucocorticoid receptor systems are being investigated. (RPIS 9258)

535. Preparation of Radiopharmaceuticals Labeled with Gallium and Indium

M.J. Welch

(314) 362-8435

\$175,000

This work is carrying out routine production of gallium-68 radiopharmaceuticals for initial use in pulmonary studies and evaluating the potential of using gallium-68 radiopharmaceuticals in positron emission tomography (PET) in clinical diagnostic studies. In studying the new gallium-68 radiopharmaceuticals that could be used with PET for clinical studies, researchers are emphasizing the use of gallium-68-labeled platelets. Monoclonal antibodies are being labeled with indium-111 and gallium-68 and are being evaluated in animal models; eventually, they will be evaluated in humans. An agent to measure myocardial blood flow has been developed, and researchers continue to work on new developments in new chelates and new bifunctional chelates for use as blood flow tracers as well as new chelates for labeling monoclonal antibodies. (RPIS 9629)

Environmental Research

Environmental Processes and Effects: Atmospheric Chemistry and Dynamics

Intramural DOE Laboratories

Argonne National Laboratory Argonne, IL 60439

Atmospheric Physics Section

536. Atmospheric Boundary Layer Transport and Dispersion Studies

R.L. Coulter

M.L. Wesely

(708) 972-5833

\$175,000

The transport and dispersive properties of the lower atmosphere are investigated to improve estimates of the rates at which airborne pollutants are diluted, removed by dry and wet processes, and delivered to sensitive receptors. Experimental studies are conducted with ground-based remote sensing equipment such as Doppler acoustic sounders, radar wind profilers, and laser anemometers and with direct sensing devices deployed at the surface or carried aloft by free or tethered balloons. Advanced integrated acoustic and radar systems developed at Argonne National Laboratory allow evaluation of the vertical structure of the mean and turbulent, three-dimensional wind components in the lower atmosphere, without using instruments on towers. These studies detail the diurnal variations in the planetary boundary layer and provide high resolution, continuous observations of nighttime drainage winds above complex terrain. To study transport over complex and nonuniform terrain, this research group participates in large, multiorganizational field experiments. Transport and diffusion processes are described mathematically, and these descriptions are tested against experimental data. The results of this work contribute to the development of the improved emergency response and air pollution models that are required to plan and manage energy generation and fuel conversion facilities. (RPIS 4437)

537. Atmospheric Chemistry of Organic Oxidants and Aldehydes

J.S. Gaffney

N.A. Marley

(708) 972-5178

\$180,000

This research develops a fundamental understanding of the atmospheric chemistry of organic oxidants and their precursor aldehydes. These tropospheric pollutants, produced during the transport and transformation of energy-related emissions, are of concern because of their chemical and physical environmental interactions. Such secondary organic oxidants can play important roles in gas, aerosol, and aqueous phase chemistries in the troposphere. They can also be toxic to plants and animals. Furthermore, these trace level compounds are strong infrared absorbers and may be important greenhouse gases. Organic oxidants and aldehydes under study include organoperoxy nitrates, organic peroxides and peracids, formaldehyde, acetaldehyde, and higher aldehydes. This research examines the potential effects of these compounds by making direct measurements of peroxyacetyl nitrate and aldehydes. These data are used to estimate the atmospheric levels of peracetic acid and methylhydroperoxide. Data obtained from a number of sites delineate the tropospheric levels, seasonal variability, and sources of organic oxidants and aldehydes and allow their potential atmospheric and ecological importance to be evaluated. Fourier transform infrared and laser Raman spectroscopies are used to examine the radiative properties and aqueous chemistries of these reactive toxins. Knowledge of both is needed to evaluate the importance of organic oxidants and aldehydes in tropospheric chemical issues that range from global climate change to regional oxidant problems and acid rain. (RPIS 5162)

538. Continental Dry Air-Surface Exchange

M.L. Wesely

(708) 972-5827

\$175,000

This component of DOE/OHER's atmospheric chemistry program investigates the dry air-surface exchange of energy-related trace chemicals over North America. Emphasis is on inferring the dry deposition of energy-related sulfur and nitrogen compounds at regionally representative sites with specially designed stations and computing areal averages of dry deposition as a component of mass budgets of the chemicals

over the U.S. In this way, atmospheric cleansing and delivery of trace chemicals to ecosystems are estimated. In addition to sulfur and nitrogen compounds, oxidants and organic compounds are studied because they are also important in tropospheric chemistry and ecological effects. This project consists of field measurements, theoretical studies, and parameterization of dry air-surface exchange rates. The results are applied to estimate dry deposition at the specially designed network measurement stations with site-specific models and over large areas with regional scale numerical models. Field studies primarily use micrometeorological techniques to measure the air-surface exchange rates. To compute mass budgets, natural surface sources of some of the substances must be considered when the surface sources are significant compared to anthropogenic sources. (RPIS 4436)

539. Atmospheric Chemicals' Sources and Fates

M.L. Wesely

D.L. Sisterson

(708) 972-5827

\$200,000

This project is part of the the DOE Atmospheric Chemistry Program that investigates the fate of energy-related trace chemicals in the atmosphere over continental and oceanic areas. In collaboration with Brookhaven National Laboratory, Pacific Northwest Laboratory, and a number of contracting universities and agencies, Argonne National Laboratory (ANL) studies several aspects of the atmospheric mass budgets of energy-related trace chemicals, which can influence the global climate through tropospheric pollutants, greenhouse gases, and cloud properties important in the radiation budget of the atmosphere. ANL assembles and analyzes data suitable for the mass budgets, especially aspects involving (1) large-scale integration of deposition fields in relation to both anthropogenic and natural emissions and (2) estimation of off-continent transport. In support of mass budget calculations, experimental, theoretical, and modeling research efforts by ANL are devoted to evaluating the production of nitrogen oxides by lightning fixation associated with thunderstorms and to estimating dry air-surface exchange over oceans. Lightning is a significant source of nitrogen oxides compared to anthropogenic sources, and knowledge of air-surface exchange of many substances over oceans is adequate. (RPIS 4438)

540. Atmosphere-Ocean Chemical Exchange

M.L. Wesely

(708) 972-5827

\$120,000

The project evaluates and assists in improving the ability to observe atmospheric winds, temperature, moisture, and chemical constituents by the Grumman Gulfstream (G-1) aircraft as instrumented and operated by the Pacific Northwest Laboratory and Battelle Columbus. Its products include quantitative estimates that can be compared with corresponding observations from the G-1 aircraft, particularly for the vertical fluxes of heat, mass, and momentum. Measurements of the air-surface exchange rates and associated

turbulence quantities for heat, moisture, momentum, and selected chemicals are made from a surface tower so that comparisons can be made to corresponding measurements made with the G-1 aircraft gust probe and fast-response sensors during flights near the tower. The 300-m meteorological tower maintained near Boulder, Colorado, by the National Oceanic and Atmospheric Administration (NOAA) may be used for this purpose. In addition, coordination is provided for comparisons with measurements by surface platforms that are deployed by other programs, (e.g., during one of the several tropospheric oxidant studies being conducted in the U.S.) Wingtip-to-wingtip comparisons with other aircraft are particularly valuable in evaluating the ability of the G-1 to measure both mean and turbulence qualities. Assistance is provided in arranging such comparisons, e.g., during oxidant studies or when aircraft test flights are conducted with aircraft operated by NOAA or the National Center for Atmospheric Research. In addition, Argonne personnel serve as advisors and research collaborators on the flux measurements made with the G-1 and on the chemical measurements made with the on-board trace atmospheric gas analyzer. (RPIS 5681)

Brookhaven National Laboratory

Upton, NY 11973

Department of Applied Sciences

541. Continental and Oceanic Fate of Energy-Related Air Pollutants

P.H. Daum

L. Newman

Y.N. Lee

L.I. Kleinman

(516) 282-7283

\$1,200,000

The project objective is to obtain an understanding of the atmospheric processes that control the transport, transformation, and ultimate fate of air pollutants emitted in conjunction with energy-related activities. Emphasis is on sulfur, nitrogen, and reduced carbon compounds and the oxidants that can influence their behavior. The program consists of three related components: (1) field measurements that focus on processes that redistribute pollutants and involve measurement of concentration fields of pertinent species associated with meteorological features (up to and including synoptic scales), with emphasis on concentration fields in and around storm systems; (2) laboratory studies to better understand both photochemical reactions pertinent to transport and redistribution of materials, and reactions to the transformation and removal of species by aqueous-phase reactions; and (3) theoretical studies used to provide a consistent framework to synthesize observed data and to provide input to researchers constructing large scale models. In this multilaboratory effort, Pacific Northwest Laboratory and Argonne National Laboratory are major participants with Brookhaven National Laboratory. (RPIS 4439)

542. Analysis of Aerosol Chemical and Microphysical Data in the North Atlantic Regional Experiment*P. Daum**(516) 282-7283***\$80,000**

The project's objectives are to analyze large amounts of data on aerosol microphysical and chemical properties, and in light of this analysis, plan and implement an experimental plan for aerosol measurements to be conducted during the full scale North Atlantic Regional Experiment (NARE) program in the summer of 1993. The project analyzes large amounts of data on aerosol microphysical and chemical properties from pre-NARE activities and develops an experimental plan for aerosol measurements during NARE. The primary effort of this project is to analyze the aerosol data that will be collected during NARE. Such analysis will consist of (1) characterization of the spatial distribution and composition of the aerosols, (2) characterization of the relationship between sulfate mass concentration and aerosol number densities, and (3) examination of the relationship between pre-cloud aerosol number concentrations and cloud droplet concentrations in marine stratus clouds. (RPIS 5682)

543. Atmospheric Tracer and Instrumentation Development*R.N. Dietz**(516) 282-3059***\$220,000**

This task's main objectives are the identification and use of new atmospheric tracer compounds for long-range transport studies and the support of these studies through development, validation, and application of new instrumentation. The task also supports the conceptual development and testing of tagging and tracing in areas such as subsurface transport, leak detection, fluid flow, and the technology transfer of such instrumentation and related applications. Efforts are directed at (1) the testing and validation of state-of-the-art samplers and analytical procedures for a family of perfluorocarbon tracers (PFTs); (2) the search for new PFTs with lower ambient background levels; (3) the preparation of the respective gas standards; and (4) the participation in interlaboratory testing studies, field-validation programs, and applied field studies in the respective tagging and tracing areas. An immediate objective is to demonstrate the broad range of applicability of the PFT technology to other Federal and commercial uses, with immediate emphasis on leak detection associated with National Aeronautics and Space Administration programs, the food-packaging industry, and underground storage tanks. A new, commercially manufactured, programmable sampler will be evaluated. Preliminary studies will begin on commercialization of the continuous PFT analyzer (continuously operating perfluorocarbon sniffer) and the modified real-time dual-trap analyzer with improved capability for use in urban environments. The results of this task will be (1) an improved tracer technology to assess the risk and impact of long-range atmospheric, subsurface, and oceanic transport, dispersion, and fate of energy-related pollutants, and (2) an availability of the PFT methodology in various commercial applications. (RPIS 3996)

544. Atmospheric Organic Chemistry: Investigation of Primary and Secondary Species*Y.N. Lee**(516) 282-3294***\$260,000**

This project's goal is to understand the role of organic compounds in the photochemistry of the troposphere. Organic compounds are thought to have a number of impacts, ranging from toxic and mutagenic activity to the promotion of ozone and oxidant formation. The pathways and rates of many key reactions remain uncertain, and data on ambient concentrations of associated intermediates are virtually nonexistent. This project involves both laboratory study of important processes and the development and application of field measurement techniques for key species and families of species. Interpretation of experimental results focuses on both individual compounds and processes on the role of compounds within the context of larger photochemical families, and overall photochemical activity. Examples of compounds, processes, and families being studied include: organic nitrates as part of the odd-nitrogen (NO_x) family, and the thermo- and photolytic destruction rates of organic nitrates. Another family being investigated is isoprene, methacrolein, methyl vinyl ketone, and the production of organic nitrates from methacrolein. (RPIS 3618)

545. Aerosol Chemistry and Dynamics*I.N. Tang**(516) 282-4517***\$260,000**

Aerosols play an important role in many atmospheric processes affecting the air quality, local visibility, and climate change. Both primary and secondary combustion products constitute a substantial portion of the ambient aerosol. To assess and possibly mitigate the environmental impact of pollutants released from energy-related sources, it is essential to elucidate the chemical and physical processes governing the formation and dynamic behavior of atmospheric aerosols. This research program focuses on laboratory studies to (1) characterize aerosol growth and phase transformation under ambient conditions; (2) measure thermodynamic and optical properties of concentrated solution droplets of inorganic salts, which constitute a large portion of the ambient aerosol; (3) investigate the evaporation kinetics of a droplet containing either a pure component or a volatile solute; and (4) develop experimental techniques to study gas-particle interactions. The results from the research program will lead to a better understanding of the basic mechanisms by which pollutants from energy-related activities may transform and transport in the environment. Thermodynamic and optical data obtained for aerosol particles are essential as input to mathematical models describing atmospheric processes such as acid precipitation and radiation balance. A fundamental understanding of aerosol growth will also find application in human health studies employing hygroscopic particles. (RPIS 3994)

Environmental Measurements Laboratory

New York, NY 10014

Environmental Studies Division

546. Pollutants in Deposition and the Biosphere

M. Helt

(212) 620-3623

\$1,634,000

The objective of this research is to determine the "environmental history" of energy-produced pollutants (potentially toxic to humans and biota) deposited in selected regions and ecosystems of the U.S. This objective includes determination of the following: (1) How much pollution has been deposited over the long term (i.e., precolonial through the present times)? At what rate has the pollution been deposited? What future trends may we expect? (2) Are there consistent spatial and temporal trends for pollutants deposited into different regions of the U.S.? How are these trends related to historic and projected patterns of energy usage? (3) How do anthropogenic inputs of energy-related substances compare with deposits from natural, i.e., "biogenic" sources? The results will lead to a better understanding of the environmental fate of pollutants associated with the combustion of fossil fuels. This study currently involves measuring historic changes in pollutant flux, concentration and inventory in selected regions and ecosystems of the U.S. This information is obtained through the technique of reconstructing pollution histories from the records preserved in lake sediments. Lake sediments are often a significant repository for atmospherically transported materials entering the environment. The sediments are dated by measurements of their artificial and natural radioactivity and by various non-nuclear techniques. Inorganic and organic analyses provides the chronology of human-derived pollutant inputs into the environment. Based upon these data, assessments of future pollution trends from fossil fuel usage and the natural (pre-colonial) or baseline levels are determined. Determining levels in food webs leading to humans and establishing whether significant energy-producing facilities and technologies are important sources of pollutants in the environment are all components of this research. The potential impact that these pollutants may have on humans and biota is also incorporated in the work. Among the pollutants investigated are elements and organic compounds shown to be toxic, tumorigenic, or carcinogenic to humans. (RPIS 4813)

Lawrence Berkeley Laboratory

Berkeley, CA 94720

Applied Science Division

547. Aerosol and Cloud Chemistry

T. Novakov

(415) 486-5319

\$156,000

The overall objective of this project is to study under laboratory conditions the chemical interactions of gaseous pollutants with subsaturated aerosols and cloud drops nucleated on these

particles. The motivation for these studies stems from the researcher's findings of enhanced uptake of SO_2 and NO_2 on laboratory clouds relative to that on bulk water, and the finding that aqueous reactions of NO_2 are fundamentally different in dispersed and bulk water systems. A specific objective of this project is to investigate whether the observed dispersed versus bulk differences are due to an intrinsic, possibly surface chemical, property of the dispersed high surface-to-volume aqueous systems. The approach to this study involves laboratory studies with an existing cloud chamber and also involves design of a new laminar flow reaction chamber in which monodisperse drops with diameters smaller than 10 μm will be reacted with gases of interest. (RPIS 1599)

Lawrence Livermore National Laboratory

Livermore, CA 94550

Atmospheric and Geophysical Sciences Division

548. Complex Terrain Studies

P.H. Gudiksen

(415) 422-1813

\$313,000

This project supports Lawrence Livermore National Laboratory's (LLNL's) participation in the DOE-sponsored Atmospheric Studies in Complex Terrain (ASCOT) program through field experiments, data analysis, and model application and development. The ASCOT program is designed to evaluate pollutant dispersion processes associated with terrain-dominated flows. It is an integrated program that includes field experiments and model development activities performed by various DOE and National Ocean and Atmospheric Administration laboratories. The program's initial technical focus was on pollutant dispersion associated with nocturnal valley flows, because this scenario seriously affected energy developments in the mountainous areas of the western U.S. The program also is applying its resources to support DOE's interest in improving the emergency response capabilities at the DOE nuclear facilities by developing models capable of predicting the impact of accidental releases of hazardous materials. The objective of this project is to support this mission by (1) participating in the ASCOT field experiments at Rocky Flats area office and the subsequent data analysis, (2) analyzing data acquired from previous field experiments in western Colorado, (3) operating a network of meteorological towers in the Rocky Flats area office, and (4) applying the LLNL models to the ASCOT field study for improving the understanding of terrain-dominated flows. (RPIS 3989)

549. Mesoscale Emergency Response

J.M. Leone, Jr.

(415) 422-6449

\$300,000

This task supports Lawrence Livermore National Laboratory participation in the DOE-Sponsored Atmospheric Studies in Complex Terrain (ASCOT) program through numerical model development. The ASCOT program is designed to evaluate

pollutant transport and diffusion processes associated with terrain-dominated flows. It is an integrated program that includes a wide spectrum of numerical modeling and field experiment activities performed by various DOE and National Ocean and Atmospheric Administration laboratories. The program is applying its resources to support DOE's interest in improving the emergency response capabilities at the DOE nuclear facilities by developing models capable of predicting the impact of accidental releases of hazardous materials. The objective of this project is to support this mission with five tasks: (1) improving the diffusion module in the ADPIC model, one of the core models of the Atmospheric Release Advisory Center (ARAC) emergency response service; (2) improving the initialization and turbulence parameterization schemes in our finite element-based boundary layer models; (3) applying FEM-PBL, the nonhydrostatic model, within the ASCOT experimental areas to gain improved understanding of terrain-driven circulations; (4) continuing to develop SABLE, a hydrostatic mesoscale boundary layer model suitable for emergency response calculations; and (5) coupling the ADPIC model with the finite element boundary layer models to enable improved understanding of dispersion within terrain-driven circulations, and for subsequent inclusion in the ARAC service. (RPIS 4915)

550. Modeling in Support of DOE's Participation in the North Atlantic Regional Experiment

J.E. Penner

(415) 422-4140

\$156,000

The project's objectives are (1) to use tropospheric chemistry models in support of the Pacific Northwest Laboratory G-1 aircraft measurements in the North Atlantic Regional Experiment (NARE) and (2) to develop the ability to predict oxidant concentrations in the troposphere resulting from energy-related pollutants. Before the experiment, model estimates of the expected abundance of NO, NO₂, HNO₃, DMS, SO₂, and aerosol are made using meteorological fields from the Lawrence Livermore National Laboratory version of the National Center for Atmospheric Research general circulation model, CCM1. Within the constraints of the ability to complete the development of the nucleation model, model estimates of the vapor phase of H₂SO₄ and aerosol number concentrations may be provided. These estimates are focused on the region of the G-1 flights. Because these flights are close to the source regions and because the model may inaccurately portray these regions, a number of sensitivity studies is being carried out to compare the predictions of the model for this region using different numbers of parcels, different mixing coefficients, and different algorithms for mapping concentrations from the Lagrangian parcels (which are computed by the models) to concentration ratios on the Eulerian grid. Following the G-1 experiments, predictions of the model are compared with the data collected by the G-1 and by other groups participating in NARE. If possible, this comparison is done using realistic meteorology that is specific to the timeframe of the measurements. This model/data comparison is used to check the

consistency between the understanding of the sources, transport, transformation, and loss processes of the trace species involved in the formation of atmospheric oxidants and sulfate aerosol. The comparison is also used to plan a more comprehensive field experiment in the future. (RPIS 5683)

Los Alamos National Laboratory

Los Alamos, NM 87545

Earth and Environmental Sciences Division

551. Terrain-Influenced Meteorology

W.E. Clements

J.T. Lee

J. Bossert

(506) 665-2637

\$560,000

This research responds to two national needs: developing new energy resources and a credible emergency response capability for accidental atmospheric releases of hazardous material. A fundamental understanding of atmospheric transport, diffusion, visibility, and deposition is related to these potential problems is essential. Potential sources are frequently in areas where the meteorology is dominated by terrain variability. It is necessary to develop new techniques for data measurement and analysis and new methods for estimating transport for sites in areas of complex terrain. The DOE Atmospheric Studies in Complex Terrain (ASCOT) program addresses these needs. In the past, the program has concentrated on locally driven nighttime circulations in valleys. Consistent with the program's long-range plan of systematically expanding its studies to regional and larger scales, ASCOT has begun investigating multivalley and valley-plain systems. The program emphasizes theory, experiments, laboratory simulations, and numerical modeling. Results include the successful simulation of airflow in several valleys with different topography and vegetation. The interpretation of field data yields a consistent picture of the budgets of mass, momentum, and energy in the locally driven nighttime valley circulation. The skill of tracer concentration estimates is approaching the levels for the much simpler flat terrain. By channeling this expanded knowledge through numerical models, capabilities will be extended to generalized topography and meteorology with a minimum of onsite data. (RPIS 4163)

Oak Ridge National Laboratory

Oak Ridge, TN 37831

Environmental Sciences Division

552. Atmosphere-Canopy Interactions

S.E. Lindberg

(615) 574-7857

\$200,000

This research program is directed toward understanding the mechanisms of air-surface exchange and quantifying the rates of wet and dry removal and surface emission rates of the natural

and pollutant constituents related to energy production, which are important to atmospheric chemistry and to biogeochemical cycling. Emphasis is on determining the interactions of these materials with forest canopies. This work supports DOE tasks in the Atmospheric Chemistry Program, including aerosol chemistry, trace gases, dry deposition, modeling, landscape scaling, biogenic emissions, precipitation scavenging, fate of air toxics, and biogeochemical cycles. Specific tasks include (1) developing and applying surface analysis and canopy scaling methods to measure deposition to forests in regions of complex terrain; (2) applying profile methods and resistance models to quantification of the atmosphere-surface exchange of Hg vapor; (3) testing new methods for the real-time analysis of hydrocarbons in the canopy airspace; (4) determining the behavior and speciation of vapor-phase metals in combustion plumes; (5) testing throughfall model assumptions on the behavior of sulfur and nitrogen using isotopes; (6) modeling the kinetics of rain-canopy interactions; (7) determining the relationships among air and rain chemistry and meteorology for trace metals; (8) measuring trends in wet deposition to the Walker Branch Watershed from the Oak Ridge NADP/NTN site in support of biogeochemical cycling studies; and (9) collaborating with the Institute of Terrestrial Ecology in Edinburgh, United Kingdom, the University of Utrecht, and the Institute of Bioclimatology in Göttingen, Federal Republic of Germany, on the deposition and canopy interactions of nitrogen and sulfur in forests in North America and Europe. (RPIS 1624)

Pacific Northwest Laboratory **Richland, WA 99352**

Atmospheric Sciences Department

553. Atmospheric Diffusion in Complex Terrain

K.J. Allwine

(509) 375-8145

\$174,000

The object of the Atmospheric Diffusion in Complex Terrain (ADICT) program is to identify and study the forcing mechanisms that determine the structure and evolution of wind and temperature fields in regions of complex terrain so that their effects on the transport and dispersion of atmospheric pollutants can be evaluated and predicted. Such studies are required to (1) assess realistically potential and actual environmental impacts arising from utilization of energy resources, (2) analyze and predict the fate of pollutants released routinely or accidentally into the atmosphere, and (3) further understanding of fundamental meteorological processes in the atmospheric boundary layer. As part of DOE's Atmospheric Studies in Complex Terrain Program, ADICT researchers pursue these goals through a combination of measurements, data analysis, and numerical experiments with sophisticated mesoscale computer models. This research has contributed to understanding of the (1) transport and dispersion of pollutants in mountain valleys, (2) interaction of ambient and locally generated wind systems, (3) effects of local and regional terrain on the structure and evolution of wind patterns, and

(4) strengths and limitations of emergency preparedness codes. Recent areas of investigation have centered on the Tennessee Valley, Colorado's Front Range near the Rocky Flats Site, and the Hanford Site in Washington. Current and future emphases focus on the development and use of improved computer codes that can further the ability to describe meteorological behavior in regions of complex terrain. (RPIS 4174)

554. DOE Atmospheric Chemistry Program Management

W.R. Barchet

(509) 375-7373

\$170,000

This project provides scientific management and leadership for the DOE Atmospheric Chemistry Program (ACP). It produces the atmospheric-chemistry information necessary to implement specific requirements of and for progressive modification of the National Energy Strategy. The project aims to (1) elevate DOE's atmospheric chemistry program so that DOE is fully recognized as a scientifically respected and equal participant in the global atmospheric-chemistry research community, (2) coordinate the atmospheric-chemistry efforts at the DOE laboratories so that their composite contribution maximizes benefit to DOE, and (3) focus on DOE laboratory activity in atmospheric chemistry so that it maximizes response to the needs set forth in the National Energy Strategy.

Subtask 1: Program Restructuring and Implementation addresses the needs for program reorientation and design to directly fulfill the needs associated with the new National Energy Strategy. Activities include (1) developing a conceptual and interactive design of the forthcoming scientific research plan and implementing its management and accountability structure, (2) planning and implementing an ACP peer review, (3) planning and implementing a DOE university grants program in atmospheric chemistry, and (4) creating and implementing a program plan document for formal implementation of ACP.

Subtask 2: Scientific Program Monitoring and Leadership is a continuing scientific program monitoring effort. Activities include (1) implementing of the programmatic adjustments necessary to ensure focused and timely performance of the program, (2) organizing external peer reviews at scheduled intervals, (3) providing basic program leadership and implementing the joint planning and decision making process, and (4) coordinating major program changes, when they become necessary. Success of the DOE ACP will depend on its being strongly interactive with external scientific entities, both at the planning and implementation levels.

Subtask 3: Research Oversight involves initiating small development projects critical to the evolving program but not foreseen in the program's overall scientific design. These projects are intended to respond to previously unforeseen but currently anticipated program needs. (RPIS 4751)

555. North Atlantic Regional Experiment Field Campaign

W.R. Barchet

(509) 375-7373

\$400,000

The project is designed to make extensive use of the G-1 aircraft, carrying the trace atmospheric gas analyzer mass spectrometer and the static-port gust probe, as well as various additional monitoring equipment, in the 1992 summertime field campaign associated with the IGAC North Atlantic Regional Experiment (NARE). Its products include: (1) characterization of aerosols and their nucleation and growth rates over the Atlantic, (2) characterization of North Atlantic pollutants for interpretation of maritime pollutant behavior and for global chemical model development, and (3) measurement of oceanic pollution emissions and deposition. The flight plans for NARE 1992 are coordinated with National Oceanic and Atmospheric Administration surface station operations on Sable Island, Cape Race, and elsewhere. The first of two primary plans involves a dog-leg pattern beginning at Halifax and proceeding due south to a point due east of Nantucket, followed by a trace west to Nantucket. This pattern is reversed on return flights. Two of these flights are expected to be conducted on days when this pattern is flown. The second primary plan involves a straight pattern flown from Halifax to Sable Island. Vertical pollution characterization is a primary motivation for this pattern, with a linkage of aircraft observations to the surface measurements on Sable Island. (RPIS 5684)

556. Continental and Oceanic Fate/Air Pollutants

C.M. Berkowitz

(509) 375-6460

\$525,000

Continuing the program of coordinated DOE multilaboratory atmospheric chemistry research, the Continental and Oceanic Fate of Energy-Related Air Pollutants Project is approaching the problems associated with the effects of energy-related air pollutants on the global environment. The project's primary objective is to conduct applied research that will, in general, improve understanding of atmospheric processes and, in particular, provide information vital for development and implementation of the National Energy Strategy. The predecessor project, Processing of Emissions by Clouds and Precipitation, was narrower in scope, directed toward regional acidic deposition. It made, however, important strides in (1) understanding the processes by which oxidants such as H_2O_2 produce acidic deposition, (2) developing storm scavenging models, (3) obtaining comprehensive and unique field program databases, and (4) understanding the redistribution of pollutants by storm systems. The current project focuses on two areas: (1) much needed measurements of trace chemicals at unprecedented sensitivity levels (using the Pacific Northwest Laboratory G-1 aircraft and advanced mass spectrometry) and (2) development of a global chemical model that adds chemical processes to global circulation simulations. The emphasis is on developing basic tools that will contribute significantly to interagency and internationally coordinated global environment field and modeling studies. (RPIS 4440)

557. Research Aircraft Operations

K.M. Busness

(509) 375-4503

\$750,000

During the past 10 years, understanding of atmospheric radiant transport and storm and pollutant processes has advanced significantly. These advances have been caused by a simultaneous evolution of advanced diagnostic models, laboratory measurement techniques, and field-measurement instrumentation. The advances have combined with new DOE programmatic responsibilities, such as global change research, to create increased demands for reliable and versatile aircraft measurements of atmospheric chemical and physical parameters. Until recently, these measurements were largely impossible with the type of aircraft under direct DOE control. Specifically, a sampling platform that provides a high altitude measurement capability and safely and reliably penetrates storm systems for extended periods under a variety of conditions is required for long-term DOE service as an airborne atmospheric research laboratory. This function is filled by a mid-sized twin-engine turboprop aircraft instrumented for air and cloud chemistry and atmospheric physics and dynamics investigations. This project provides for a financially stable aircraft program at Pacific Northwest Laboratory that sets the stage for equipping, maintaining, and operating this aircraft. (RPIS 4750)

558. Atmospheric Studies in Complex Terrain Program: Scientific Direction

J.C. Doran

(509) 375-4734

\$165,000

The Atmospheric Studies in Complex Terrain (ASCOT) Program is a multilaboratory research effort designed to understand, describe, and predict the atmospheric boundary-layer flow over complex terrain and the highly variable transport and dispersion of contaminants released within it. The ASCOT Program Scientific Direction project promotes and coordinates cooperative research among the primary laboratories participating in ASCOT, [i.e., Argonne National Laboratory, Los Alamos National Laboratory, Lawrence Livermore National Laboratories, National Oceanic and Atmospheric Administration (NOAA)/ATDD, and Pacific Northwest Laboratory], and with other supporting NOAA laboratories and university groups. This project's approach to leading and coordinating the ASCOT effort is to define a scientific focus for the program, representing the consolidated interests of the participants and some of the most urgent challenges to the scientific community. At the same time, this project seeks to identify and link DOE's mission-related needs with ASCOT's scientific outputs. Currently, emphasis is being directed toward providing results important to emergency response needs. The project is maintaining this scientific and mission-related focus for ASCOT through (1) planning with representatives of the participating laboratories, (2) strengthening organizational components of the program, (3) promoting collaboration and exchange among scientists involved, (4) communicating directly and frequently with participants and with DOE, and (5) promoting technology transfer to user groups within DOE and elsewhere. (RPIS 5161)

559. Direct Simulation of Atmospheric Turbulence*J.C. Doran**(509) 375-4734**\$250,000*

Collaborative research between Pacific Northwest Laboratory and the University of Washington is underway to use state-of-the-art direct simulations to study basic problems in geophysical turbulence and diffusion. The project is employing models capable of performing full turbulence simulations (FTSs) and large eddy simulations (LESs) of a variety of important turbulent processes. FTS methods are being used to study turbulence and mixing in stably stratified shear layers, such as those found in the oceans and atmosphere. Additionally, wave-turbulence interactions and atmospheric radiative transfer-turbulence interaction in stably stratified boundary layers are being simulated to ascertain the properties of this poorly understood regime. LES calculations are being carried out to study turbulence and concentration fluctuations in neutral and convective atmospheric boundary layers. The simulation of turbulence and diffusion is providing improved predictive capabilities that can be applied to problems in (1) emergency management of accidental releases, (2) transport and diffusion of pollutants in the boundary layer, and (3) mixing and chemistry in stably stratified environments. FTS and LES models are being devised to take advantage of the massively parallel computing platforms currently being developed, which are expected to provide 1,000 times greater throughput than existing supercomputers within 5 to 10 years. (RPIS 5226)

560. Interactions Between Surface Exchange Processes and Atmospheric Circulations*W.J. Shaw**(509) 375-4603**\$150,000*

The object of the Interactions Between Surface Exchange Processes and Atmospheric Circulations program is to study the (1) effects of surface exchanges of heat, momentum, and moisture on the generation of circulation patterns in the atmospheric boundary layer and (2) possible feedback of these circulations on the surface processes. An integrated program of numerical modeling and field measurements is providing the tools necessary to increase our understanding of the complex relationships among these phenomena. The program is also providing information useful for studying the dependence of plant and soil characteristics on wind, humidity, and temperature patterns. Such information is necessary to evaluate the effects of possible climate changes on local and regional environments. It also contributes to the development of realistic subgrid-scale parameterizations for use in global climate models. (RPIS 5227)

561. Coupling/Decoupling of Local and Synoptic Circulations*C.D. Whiteman**(509) 375-8639**\$224,000*

A basic research program is being conducted to investigate the interactions among atmospheric circulations of different scales. The initial research emphasis is on the physical mechanisms by which thermally developed circulations become coupled during daytime and decoupled during nighttime, from larger scale systems above an area of complex terrain. A quantitative understanding of these mechanisms is being used to improve the performance of existing emergency response, and environmental transport and assessment models for air pollution dispersion in areas of significant terrain influence. The research program includes field experimentation, data analysis, and mathematical modeling. Hypotheses and research approaches are developed on the basis of field studies, including those conducted in the large, multi-DOE-laboratory component of the Atmospheric Studies in Complex Terrain field program. Research includes investigation of the basic physics of atmospheric flows of different scales including along-slope, along-valley, and other thermally forced circulations. The thermal driving forces for such flows are investigated directly by determining the energy balances of sloping surfaces and the related fluxes of atmospheric mass, energy, and momentum. Mathematical models are used to simulate the complex thermodynamic and dynamic interrelationships between local and synoptic circulation systems. (RPIS 3879)

Westinghouse Savannah River Company
Aiken, SC 29802

Savannah River Technology Center**562. Atmospheric Transport of Contaminants***R.P. Addis**(803) 725-3325**\$200,000*

This program aims to develop, evaluate, and improve mathematical models to calculate transport, diffusion, and resuspension of atmospheric pollutants released from point sources. It combines knowledge of transport processes in the atmosphere, water, soil, and biological systems into a unified theory of pollutant cycling in the environment.

The program utilizes extensive meteorological data from the WJBF and Area Tower System, Central Climatology Station, WIND computer, and AFOS system, together with comprehensive facilities of the TRAC mobile laboratory and a trace gas analysis laboratory. Recently acquired Doppler echosondes have extended these capabilities. Project emphasis is to study dispersion in the stable (nocturnal) planetary boundary layer where the highest concentrations of pollutants can be brought from aloft to the Earth by intermittent turbulence. Emphasis is also given to flows influenced by

terrain features. The STABLE (STABLE Boundary Layer Experiment) project efficiently utilizes resources from university and DOE-affiliated laboratories during a series of field programs and model evaluation studies of the stable boundary layer. The STABLE field program has been bolstered with the addition of a second continuous SF-6 analyzer. This analyzer was installed in a second vehicle, independent of TRAC, to aid plume detection and plume spread studies. Work continues on the development of a local and regional scale three-dimensional wind field and dispersion model for mesoscale wind and dispersion predictions for emergency response. Modification to the WIND system codes will be made based on the results of analyzed data from STABLE and MATS experiments. Work is to begin on incorporating (1) the WIND tower data and Doppler echosonde data into the three-dimensional wind field and boundary layer models; and (2) new sources of wind data into the regional wind field code. Several sources of wind data exist from nuclear and fossil fuel powerplants and chemical plants. Means to use these and other sources of data to improve model performance are to be explored. (RPIS 672)

Environmental Processes and Effects: Atmospheric Chemistry and Dynamics

Offsite Grants

Boston College
Chestnut Hill, MA 02167

Department of Chemistry

563. Measurement of Gas-Water Uptake Coefficients for Trace Gases Active in the Marine Environment

P. Davidovits

(617) 552-3617

\$106,000

The objective of this project is to measure air-water exchange coefficients of specific gases that are of importance in the marine atmosphere. Interphase transport of trace gases between the gaseous and aqueous phases represents an important internal calculation of atmospheric chemistry models. Specific aspects of this interphase exchange, however, remain poorly understood and result in a major uncertainty in model predictions. The measurements of air-sea exchange provide the basis for model improvement.

The approach to the research uses an existing apparatus that has been applied successfully other gases in past work. Specifically, measurements of uptake coefficients on aqueous droplets are performed for reduced sulfur species, including

dimethyl sulfide, hydrogen sulfide, carbon disulfide, methyl mercaptan, and their oxidation products, including carbonyl sulfide, methane sulfonic acid, dimethyl sulfoxide, and dimethyl sulfone. The uptake coefficients are measured over a sufficient range of conditions to provide both the mass accommodation coefficient and the solubility parameters for these species. Measurements are done as a function of temperature, pH, and ionic strength. (RPIS 10508)

Measurements of uptake coefficients on aqueous droplets are also being performed for ozone, NO, NO₂, and NO³. As in the instance of reduced sulphur species, measurements are being acquired over a range that provides both the mass accommodation coefficient and the solubility parameters for these species. Measurements are done as a function of temperature, pH, and ionic strength. (RPIS 10508)

Comstock, Inc.
Oak Ridge, TN 37831

564. Detection of Atmospheric Pollutants Using Infrared Lasers Produced by Stimulated Electron Raman Scattering

J.E. Talmage

(615) 483-7690

\$497,652 (2-year funding)

The purpose of this study is to establish the potential for rapid response, high resolution detection, and characterization of infrared active environmental pollutant molecules. Phase I indicated that it is feasible to use stimulated electronic Raman scattering (SERS) radiation for the detection of pollutants important in greenhouse effects and acid rain. SERS-generated pulsed tunable infrared (IR) laser beams appear to offer an excellent opportunity for improved instrumentation in such areas as remote measurements, localized sensing, and high sensitivity detection, and may be used in extreme pressure and/or temperature environments. Integration of an optimized optical heat pipe with a pulsed dye laser should result in an effective extension of dye laser range into IR. These Phase I results lead, in Phase II, to a method that is sufficiently general and sensitive to detect, identify, and quantify both known and as yet unknown pollutants in the environment. Phase II studies the development of two new, high resolution IR spectrometers based upon the generation of tunable IR laser light from SERS in metal vapor heat pipes. Visible light from a pulsed tunable dye laser (or broadband amplified stimulated emission) is used to resonantly or near-resonantly excite metal vapors contained in an optical heat-pipe that is then used to generate tunable (or broadband) IR light. One of the spectrometers consists of a tunable, laser-based SERS-IR source using a high resolution, low divergence, tunable dye laser to generate an ultra-high resolution tunable IR laser beam. The second utilizes broadband, high intensity, pulsed IR light produced from broadband SERS generation that results in a time-resolved IR absorption spectrometer based upon a multi-element mercury-cadmium-telluride array. These IR laser-based instruments should be useful in numerous basic and applied research areas.

The tunable IR can be used to detect acid rain pollutants and trace greenhouse gases over extended distances in the atmosphere. The broadband IR light source is incorporated into an IR absorption instrument capable of detecting transient species (nsec time scale). A significant fraction of dye laser users might find immediate application of these instruments. (SBIR)

University of Minnesota
Minneapolis, MN 55455

Department of Mechanical Engineering

565. Ultrafine Aerosol Size Distributions and Sulfuric Acid Vapor Pressures: Implications for New Particle Formation in the Atmosphere

P.H. McMurry

(612) 625-3345

\$93,000

The objective of this research project is to determine production rates of new sulfuric acid particles by homogeneous nucleation. Scientific understanding of the relationship between atmospheric emissions (especially aerosol precursor gases) and atmospheric aerosol size distributions is especially primitive. This project advances understanding in this area by focusing on production rates of new sulfuric acid particles by homogeneous nucleation, which may play a key role in regulating atmospheric size distributions.

The experimental program focuses on two key measurements. The first of these involves measurement of the vapor pressure of sulfuric acid at temperatures and relative humidities relevant to the atmosphere. Vapor pressures are inferred from measured evaporation rates of monodisperse ultrafine (5 to 50 nm diameter) sulfuric acid droplets. The tandem differential mobility analyzer technique is used for these measurements. This method is especially suitable for measuring ultra low vapor pressures and has been used successfully with other species. The sulfuric acid vapor pressure is a key variable for determining nucleation and growth rates.

The second key measurement pertains to the size distribution of ultrafine aerosols. An ultrafine aerosol condensation nucleus counter (UFACNC) of is being used for these measurements. Measurement techniques involve measuring the UFACNC pulse height distribution as a function of particle size and varying the size-dependent cut point of the instrument by adjusting its condenser temperature. The ultrafine aerosol particle distributions thus obtained provide important information on rates of homogeneous nucleation. (RPIS 10509)

National Oceanic and Atmospheric Administration

Oak Ridge, TN 37831

Atmospheric Turbulence and Diffusion Division

566. Atmospheric Turbulence and Diffusion Research

R.P. Hosker, Jr.

(615) 576-1248

\$250,000

The objectives of this project are to (1) develop better methods of describing atmospheric transport, diffusion, and deposition in numerical simulations; (2) extend the applicability of these techniques to nonideal situations such as nonstationary conditions, complex terrain, and dense vegetation; and (3) develop and test improved numerical models incorporating these new methods. Predictive capabilities are being developed using the results of this research.

The first component of the research approach involves dispersion and planetary boundary layer studies. This work extends contemporary understanding of transport and dispersion in the lower atmosphere to nonstationary conditions. It also provides improved methods for measuring atmospheric plume dispersion rates and for including realistic dispersion parameters in numerical models. Current activities focus on the role of wave/turbulence interaction and sporadic nocturnal turbulence as mechanisms for accelerating dispersion at night and on the consequences of release of dense and/or chemically reactive pollutants.

Canopy micrometeorology is the second component of the research approach. This research effort is designed to identify and quantify the interactions involved in above- and within-canopy transport, dispersion, and deposition in canopy-atmosphere exchanges of materials and energy. The resulting information is used to include and/or parameterize physical and biological surface effects in numerical models ranging from local to global scales.

The third component of the approach is dry deposition. A core network of three research sites has been set up under joint DOE, National Oceanic and Atmospheric Administration, and Environmental Protection Agency sponsorship. These sites provide reference data for a more extensive network of routine air-concentration and meteorological monitoring stations established as core/satellite stations. Parameterizations developed in this program are used to interpret data obtained in field applications of the "concentration monitoring" approach to dry deposition monitoring.

Physical modeling is the fourth component of the research approach. Contemporary mathematical models of plume dispersion are not yet adequate to calculate concentrations of pollutants when the plume is affected by hills and buildings. Small scale models immersed in the flow of a wind tunnel or water channel (i.e., fluid models) can frequently be used to simulate transport and diffusion in a timely and relatively inexpensive manner. A wind tunnel is available for modeling studies in conjunction with Atmospheric Turbulence and Diffusion Division programs. (RPIS 0532)

567. Complex Topography in Atmospheric Studies in Complex Terrain

R.P. Hosker, Jr.
(615) 576-1248

\$297,000

The objective of this research is to design, plan, and conduct field experiments with other participating Atmospheric Studies in Complex Terrain (ASCOT) laboratories. These field experiments investigate mesoscale circulations in areas of complex terrain and the dispersion of contaminants released within them. Investigators are analyzing meteorological and turbulence data and tracer concentrations measured in ASCOT experiments in order to improve understanding of the characteristics of flow and dispersion in complex terrain. Utilizing these data, researchers are developing and evaluating numerical models of flow and dispersion in drainage flows in complex terrain.

Databases characterizing the complex airflow and dispersion over nonuniform terrain under varying conditions of thermal and mechanical forcing and influences of multiscale interactions between local, regional, and synoptic flow fields have been constructed. Useful physical concepts and hypotheses that have been tested utilizing these databases are also being produced. Investigators are creating validated numerical models of flow and dispersion in complex terrain that can be used for research, parameterization studies, safety and risk assessment, and regulatory applications.

Meteorological measurements are taken to characterize mesoscale circulations and the fluxes that determine their evolution. Sodar, tethered sonde, airsonde, and other sounding instrumentation provide periodic profiles of wind speed and direction, temperature, humidity, turbulence, and certain trace gases. Tower networks continuously detect near-surface variables and gradients that, together with turbulent flux instrumentation and radiometers, provide surface energy budgets and other exchanges between atmosphere and surface as well as their spatial and temporal variabilities. Flux and turbulence measurements from low flying aircraft also provide both horizontal and vertical variations important to scale interaction studies and evaluations of flux divergences and wave generation.

Concentration data from two nights of the 1984 ASCOT tracer experiments in Brush Creek Valley, Colorado, are being analyzed to develop a time sequence of concentration isopleths along and across the valley axis. The results are explained in terms of tracer release height, topography, winds, etc. A variety of statistical techniques are being applied to investigate the adequacy of wind fields derived by interpolation between measurements at a few sites near the emissions source for use in puff models of pollutant transport over moderately complex terrain. Detailed wind data collected during the 1990 ASCOT experiment in the Oak Ridge, Tennessee, region are being analyzed for this study. (RPIS 4589)

University of Pittsburgh
Pittsburgh, PA 15260
Department of Chemistry**568. Characterization of Gas-Aerosol Interaction Kinetics Using Morphology-Dependent Stimulated Raman Scattering**

P.M. Aker
(412) 624-0500

\$83,000

The objective of this project is to develop the morphology-dependent stimulated Raman scattering (MDSRS) technique to attain significantly increased sensitivity levels.

The heterogeneous reactions of pollutants on the surfaces of (or within) aerosol particles are a major uncertainty in atmospheric chemistry. Progress in this area has been limited by the unavailability of measurement techniques that can probe these processes in a specific manner with sensitivities appropriate to atmospheric concentration levels. The product of this research provides a measurement technique addressing this uncertainty.

This project adds to scientific understanding in development of the MDSRS technique to attain sensitivity levels that are much higher than those obtained during previous measurements. The experimental measurements being conducted under this program apply the enhanced MDSRS technique to measure reaction and/or condensation rates of sulfur and nitrogen gases (SO_2 , dimethyl sulfide, HNO_3) on the surfaces of water, ice, and sulfuric acid particles.

The intensity of Raman scattering is amplified appreciably when the exciting radiation's frequency is near that of an electronic transition. In essence, this sensitivity enhancement is accomplished by applying shorter wavelength radiation, thereby approaching electronic transition frequencies. (RPIS 10728)

Southwest Sciences, Inc.
Santa Fe, NM 87501
569. Fast Response Instrumentation for Methane Flux Measurements

A.C. Stanton
(505) 984-1322

\$497,792 (2-year funding)

Methane plays an important role in the chemistry of both the troposphere and stratosphere, and its increasing concentration may have important effects on the global environment. The development of improved instrumentation for real-time measurement of methane fluxes is crucial to characterizing the sources and sinks of this species. This project involves instrumentation based on near-infrared absorption using a commercial laser diode operating near room temperature. An exceptionally rugged and compact instrument for field use can be designed by using fiber optics in place of most conventional optics. Use of high frequency laser detection methods should

provide a sensitivity of 1 percent of the average ambient methane background, with 10 Hz response. An advantage of this method is that simultaneous water vapor measurements can be made with the same instrument; this allows methane measurements to be corrected automatically to dry air mixing ratios. In Phase I, a breadboard diode laser instrument demonstrated the detection of ambient methane. Phase II involves optimizing sensitivity and time response so the performance parameters needed to measure methane flux by eddy correlation methods can be achieved. A prototype instrument capable of simultaneous methane and water vapor measurements is being developed. This instrument is used in Phase II to demonstrate measurements of methane fluxes in field environments such as wetlands, rice paddies, or landfills. This program should result in the development of a compact instrument for real-time measurement of fluxes on methane and water vapor for use in atmospheric research. Such instrumentation could also be applied to mine safety monitoring, natural gas leak detection, or combustion process monitoring and control. The techniques under study are not limited to methane but are generic to many gas monitoring applications in research and industry. (SBIR)

Spectral Sciences, Inc.
Burlington, MA 01803

570. A Diode-Laser Absorption Remote Concentration Sensor

N. Goldstein

(517) 273-4770

\$499,812 (2-year funding)

This project addresses the need for sensitive, species-selective field instruments for the remote monitoring of trace gas concentrations over long open-air paths. Such instruments are required for a large number of scientific and industrial applications in the areas of pollution monitoring and control, meteorology, and atmospheric chemistry. This project involves the development of a diode-laser absorption remote concentration sensor (DARCS) for measurement of trace gas column densities between a transceiver unit and a distant retroreflector. Wavelength-modulation and harmonic-detection techniques provide automatic control of the diode laser wavelength, as well as highly sensitive measurement of absorption by a single spectral line. The use of a single, narrow line leads to high selectivity for the species being measured. The low cost, small size, and high reliability of the near-infrared diode lasers, which are used extensively in fiberoptic communications and digital storage and readout systems, permit the DARCS system to be packaged as a portable and potentially inexpensive field instrument. In Phase I, a laboratory DARCS system was constructed using AlGaAs diode lasers, and the feasibility of measuring the concentration of minor atmospheric components over kilometer distances and with sub-ppm detection limits was demonstrated. In Phase II, a brassboard prototype sensor is developed that is suitable for field measurements of a single atmospheric trace species. This prototype is used to test the DARCS sensor concept for a

variety of trace gases using both AlGaAs and InGaAsP diode lasers. Field trials will then be conducted on a single atmospheric trace species. The DARCS sensor combines the benefits of low cost, selectivity, sensitivity, portability, and long-term unattended operation, representing a significant advance over currently available commercial instruments. The Phase II prototype sensor could be used for monitoring pollutants such as nitrogen dioxide and formaldehyde mandated by the Clean Air Act; for research in the temporal variability of climatologically important species such as carbon oxysulfide, carbon dioxide, or methane; for monitoring of emissions from waste dumps, oil fields, and industrial plants; and as an alarm system for the fugitive emissions of toxic gases such as hydrogen halides, cyanides, and ammonia. (SBIR)

State University of New York
Old Westbury, NY 11568

Chemistry/Physics Department

571. Atmospheric Peroxides

J.B. Weinstein-Lloyd

(516) 876-2743

\$82,000

This project aims to determine the aqueous-phase free-radical chemistry, where scientists have only a threshold understanding. Laboratory experiments are performed and field measurements are used to investigate the occurrence and behavior of aqueous-phase peroxides and their free-radical and ionic precursors (HO , HO_2 , O_3^-). A newly developed method for determining hydrogen peroxide is to be field tested and applied to the analysis of samples for hydrogen peroxide and organic peroxides. Low intensity ^{60}Co gamma radiation is being employed to generate radicals representative of ambient concentrations to determine reaction rates and mechanisms associated with peroxide formation. (RPIS 10510)

Texas A&M University
College Station, TX 77843

Texas Engineering Experiment Station

572. Atmospheric Aerosol Microphysics Formation, Characterization, and Interaction

W.H. Marlow

(409) 845-2271

\$108,000

Atmospheric aerosols play a significant role in determining the consequences of air pollution, through effects on the Earth's radiation balance, visibility, cloud formation, human health, and ecological systems. Because knowledge on the formation and metamorphosis of fine aerosol particles is limited, considerable uncertainty is associated with such modeling endeavors. This research aims to help reduce this uncertainty. It develops the theoretical/mathematical foundations for describing the formation and metamorphosis of ultra-fine aerosol particles, i.e., aerosol particles in the size fraction ranging between molecular clusters up to 50 nm in radius.

Research is divided into primary and secondary tasks. In task 1, calculational procedures are developed to describe the collision rates of particles. These procedures are then applied to the formation of irregular particles from noncoalescing primary particles. The results are used to characterize, in mathematically general terms, realistic atmospheric particles. In task 2, the thermodynamics of condensation on chains of 0.1 micrometer particles is calculated. Though the tasks are initially distinct, task 1 lays the foundation for future calculations of condensation on smaller particles than can be treated by the methods currently available. (RPIS 10511)

Environmental Processes and Effects: Ocean Margins

Intramural DOE Laboratories

Brookhaven National Laboratory Upton, NY 11973

Oceanographic and Atmospheric Sciences Division

573. Coastal Productivity

P. Falkowski
(516) 282-2961

\$200,000

The effects of energy-related pollutants on ecosystems of the northeast Continental Shelf cannot be assessed or predicted without an understanding of the production and fate of phytoplankton. Phytoplankton, because of their high productivity, play a central role in the flux of organic matter and pollutants. This task is studying processes that govern the production and fate of phytoplankton in coastal plumes and Continental Shelf environments.

The approach is multidisciplinary, involving shipboard observations, remote sensing, and moored instruments. The results from the second Shelf Edge Exchange Processes field program—which measured primary production, phytoplankton abundance, and oxygen production and consumption in Continental Shelf and slope waters off the Delmarva Peninsula—are being examined. Then data will be used to construct a particle-and-carbon budget to predict the source and potential future of energy-related byproducts.

Field and laboratory studies to obtain basic information on the effects of light energy and nutrients on phytoplankton growth and distribution are underway. This information will be used to develop a unified theory of the structure and function of coastal ecosystems. (RPIS 1370)

574. Molecular Ecology of Phytoplankton Photosynthesis

P. Falkowski
(516) 282-2961

\$151,000

Phytoplankton photosynthesis accounts for about 40 percent of the total global carbon fixation. Of this, it is estimated that between 25 and 50 percent of phytoplankton production occurs on continental ocean margins. Discovering what controls and limits phytoplankton production and biomass in general and on continental margins in particular is crucial to understanding the ocean carbon cycle and its relationship to other major biogeochemical cycles. Using a combination of biophysical techniques (especially pump and probe fluorescence) and molecular biological techniques (especially immunoassays) researchers are investigating the mechanisms by which phytoplankton photosynthesis responds to variations in water column physical and chemical properties. In particular, investigators are focusing on what controls the observed variations in the functional absorption cross section of photosystem II, the quantum yield of photosynthesis, and the minimum turnover time of electron transport at light saturation. Researchers are also examining how individual limiting factors evoke specific molecular markers in a variety of species and attempting to develop a battery of diagnostic markers to identify limiting factors in natural phytoplankton communities. This research will provide a fundamental understanding for developing the next generation of phytoplankton production models used to calculate carbon fluxes. (RPIS 5665)

575. Coastal Transport and Diffusion

C.N. Flagg
(516) 282-3128

\$215,000

Physical forcing of many kinds is fundamental to carbon cycling in the ocean, particularly in the shallow, confined waters of the Continental Shelves. Important processes include air-sea exchange of gases, heat, and momentum; transport of carbon and nutrients along and across isobaths; stratification and its impact on vertical mixing; formation and maintenance of surface and bottom boundary levels; and, in the Mid-Atlantic Bight, persistence of the shelf/slope front, a partial barrier to free exchange of shelf and slope waters. Areas to which Brookhaven National Laboratory oceanographers can make substantial contributions include water mass interactions, biophysical interactions, air/sea fluxes, internal wave-mediated mixing, and frontal dynamics. Water mass interactions are vitally important to studies of the exchange of material between shelf and open ocean. They are used to identify sources and sinks as well as rates of mixing, and they will be particularly useful in any study of carbon export. Advances have been made in understanding biophysical interactions, but considerable work remains. Experience in the Shelf Edge Exchange Processes II program has yielded clear ideas about how to take measurements of biophysical processes; it remains now to put the concepts into practice. Combining these measurements with appropriate analytical methods can lead to

substantial progress in understanding carbon cycling rates and their mediation by the physical environment. Numerical models will play an increasing role in unraveling the biophysical interactions. (RPIS 913)

576. Microbial Processes in Coastal Marine Systems

P. Kemp

(516) 282-7697

\$200,000

The function of DOE-funded microbial research at Brookhaven National Laboratory is to examine microbially mediated transformations of recently fixed organic carbon with a nonexclusive emphasis on benthic processes. Research activities include measurements of microbial growth and production, degradation of organic matter, oxygen consumption, remineralization end-products, and microbial interactions with other microbes and with the physical environment. Specific examples of basic measurements and activities include bacterial production and protistan grazing rates in the water column and sediment as well as interpretation and modeling of near-bottom oxygen records (moored sensors).

The current paucity of methods for microbial research demands that the Microbial Processes program include a primary emphasis on developing new and innovative methods. Current research is focused on the application of molecular biology methods to both water-column and benthic systems, specifically for measuring cell-specific, taxon-specific microbial growth rates. In addition, new procedures for simultaneous measurements of bacterial growth and biomass turnover in sediments are being tested. (RPIS 5309)

577. Measurement of Marine Microbial Growth

P. Kemp

(516) 282-7697

\$113,000

DOE has identified the development and application of molecular biology methods for examining coastal ocean processes as an important element of its Ocean Margins Program. Under a short-term exploratory research grant, investigators began examining the feasibility of a new approach for estimating microbial growth rates using oligonucleotide hybridization probes for ribosomal RNA (rRNA). The approach is based on the textbook correlation between growth rate and RNA content in cultured bacteria. The available data suggest that this correlation is robust, is applicable to marine bacteria, and extends at least to rates comparable to mean growth rates of bacteria in coastal ocean systems. Researchers are working to (1) develop field methods for in situ growth rate measurements of marine bacteria based on cellular rRNA content, (2) establish the sensitivity and reproducibility of the proposed methods, and (3) intercalibrate these methods with existing, commonly used procedures including tritiated thymidine incorporation. (RPIS 5664)

578. Food Chain Dynamics

S.L. Smith

(516) 282-2835

\$400,000

Continental shelves of the world ocean contain highly productive ecosystems associated with major fishery production and are potentially highly significant in the global cycling of carbon. These ecosystems represent the most important link between human populations and the world ocean, and they are particularly vulnerable to the effects of human-kind's energy-related activities (pollutant emission, possible climate change). The high rate of carbon cycling by such ecosystems implies the possibility of significant feedback effects involving the level of atmospheric CO₂. The Continental Shelf between Cape Hatteras and Cape Cod is a typical temperate shelf ecosystem from which it is possible to generalize processes that regulate production and biogeochemical cycling of carbon. The Food Chain Dynamics Group is developing an understanding of fundamental processes controlling coastal trophodynamics and biogeochemical cycling in order to assess the potential impacts of natural and anthropogenic perturbations.

This has led to an integrated field program that includes physical parameters; physical and biological controls of CO₂, nutrient, and oxygen levels, and the role of zooplankton distribution, growth, reproduction, and grazing for carbon fluxes. A large, diverse data set was collected during the Shelf Edge Exchange Processes II experiment. This experiment off the Delmarva Peninsula employed instrumentation moored over the shelf and upper slope for 15 months (1988-1989) and ship-based studies of process rates. Interpretation of the data collected has demonstrated the utility of several new approaches to the study of shelf biogeochemistry and ecology. (RPIS 1303)

579. Moored Sensing Systems

C.D. Wirick

(516) 282-3063

\$152,000

Natural biogeochemical processes occurring on the continental margins of the U.S. may affect the global climate. The Ocean Margins Program is assessing the quantitative significance of the continental shelves as a sink for atmospheric carbon dioxide. Carbon fixed by primary production on the continental shelves can potentially be sequestered on the shelves or transported to the ocean basins. Understanding the carbon cycle on the margins requires that primary productivity be measured with high spatial and temporal resolution and that natural variability in primary production be parameterized with regard to environmental factors such as nutrient availability, irradiance, and temperature. A prototype moored instrument capable of measuring primary production is being developed. This new instrument and the moored fluorometers developed for the Shelf Edge Exchange Processes program will be deployed in upcoming ocean margins field experiments to quantitatively describe and clarify the production, oxidation, and transport of organic carbon on continental shelves. (RPIS 4998)

580. Fast Repetition Rate Fluorometer for Making In Situ Measurements of Primary Productivity*C.D. Wirick**(516) 282-3063**\$170,000*

Understanding the ocean carbon cycle and forecasting changes in the ocean productivity require that primary productivity be measured with high spatial and temporal resolution and that natural variability in primary productivity be parameterized with regard to environmental factors such as nutrient availability, irradiance, and temperature. These researchers are developing a methodology and instrumentation to measure primary productivity from the stimulated *in vivo* fluorescence of phytoplankton and to relate the phytoplankton photosynthetic properties to environmental factors. The instrumentation is based on fast repetition rate (FRR) fluorometry, which promises an efficient and robust technique for estimating the photosynthetic rates *in situ*. Moreover, the FRR methodology directly measures such photosynthetic parameters as effective absorption cross section, photoconversion efficiency, and turnover time of photosynthesis, and relates them to primary productivity. Because the photosynthetic parameters are affected by environmental factors, the link between these and primary productivity can be established. Finally, this research should benefit the oceanographic community by providing a new instrument for measuring primary productivity. (RPIS 5663)

Environmental Processes and Effects: Ocean Margins

Offsite Grants**Columbia University**

Palisades, NY 10964

Lamont-Doherty Geological Observatory**581. Development of Gas Chromatographic System for Dissolved Organic Carbon Analysis in Seawater***D. W. Chipman**T. Takahashi**(914) 359-2900**\$81,000*

Ocean margin areas are known to be biologically highly productive, as vividly demonstrated by the recent ocean color images produced from the National Aeronautics and Space Administration Coastal Zone Color Scanner and other satellite data. Although the high primary productivity observed in the shallow coastal areas appears to be largely supported by the recycling of carbon and nutrients, the particulate organic carbon

produced by biological processes plays an important role in transporting not only carbon but also associated heavy metal elements (e.g., transuranium elements) to the deep ocean regime. On the other hand, because of the recent rapid development of the dissolved organic carbon (DOC) analytical methods and resulting large changes in recent data increases of 2-3 times in the open/deep ocean concentrations, the role played by DOC in transporting carbon from coastal to deep ocean regimes requires a renewed examination.

On the basis of the recent DOC concentration data obtained in deep ocean regimes by others, the global ocean DOC carbon pool has been estimated to be as large as 5 or 10 percent of the inorganic CO_2 pool. Some researchers hold that a change in the transfer rate of carbon from the DOC pool to the CO_2 pool could cause a major change in the atmospheric CO_2 concentration which, in turn, would affect global climate. On the other hand, the available data are highly contradictory on the linkage between these pools. In the north Pacific Ocean, the DOC concentration has been observed to be inversely proportional to the apparent oxygen utilization, although this is not the case in the Atlantic Ocean. Researchers suggest that the oxygen utilization and hence the CO_2 production in deep ocean is attributed entirely to the oxidation of DOC rather than particulate carbon, as hitherto believed. Other researchers have found that the carbon-14 contents in DOC extracted from seawater show ages of several thousand years. This suggests that organic compounds in DOC are highly refractory and should not be readily oxidized to CO_2 .

It is generally agreed that DOC in open ocean seawater is produced mainly by zooplankton activities occurring in the upper layers of oceans. In coastal waters, additional DOC sources may be considered, including continental products carried into the sea by rivers and decomposition products diffusing out of sediments, because of the complex sources and large DOC concentrations in ocean margin waters as well as the importance of DOC in the oceans. (RPIS 10693)

Dynamics Technology, Inc.

Torrance, CA 90503

582. Development of a Moored Optical Instrument for Measurement of Oceanic Particle Size and Settling Rate*E. Chang**(213) 543-5433**\$500,000 (2-year funding)*

The instrument being developed in this project is designed to measure both the size and settling velocity of oceanic particles in the range of 20 microns to several millimeters. Phase I examined critical design features of the instrument. The operational instrument (Phase III) is intended for long-term moored deployment; sample integrity, biofouling, power requirements, and other considerations for this type of deployment have been considered in the design and are being implemented and tested in Phase II. The instrument design aims to alleviate many of the problems associated with instruments

developed to measure particle fluxes, i.e., sediment traps, volume-sensitive particle counters, transmissometer-based sensors, and video techniques. Specifically, the instrument (1) measures particles from 20 microns to several millimeters in size using two optical techniques (diffraction for small particles, shadowgraph for large particles); (2) improves trapping efficiency and minimizes disruption of particles by orienting the sampling chamber with the ambient flow; (3) creates a quiescent settling chamber in which direct settling velocity measurements can be made; (4) obtains samples several times a day; and (5) increases the effectiveness of antibiofouling techniques by enclosing the measurement chamber. Goals for Phase II are to design and fabricate a prototype, test it thoroughly in the laboratory using realistic particles (including aggregates), and deploy an appropriately modified prototype in the ocean. An important part of this testing includes "ground-truth" in the form of video imagery and bottle sampling.

Successful development of this particle size and settling rate instrument should provide researchers with an important new capability for understanding the complicated processes controlling the flux of particles and their constituents from the atmosphere and upper ocean to the ocean floor. Increasing interest in the greenhouse effect and the fate of carbon (e.g., the multi-agency sponsored Global Change Program), the need to measure and predict the fate of potentially harmful anthropogenic compounds, and the increased demand for long-term measurements in all areas should create increased demand for this instrument. Accordingly, a version suitable for a range of deployment scenarios should be a viable commercial instrument. (SBIR)

Florida State University Tallahassee, FL 32306

Department of Oceanography

583. Transformation Rates and Fate of Dissolved, Colloidal, and Particulate Forms of Organic Carbon in Ocean Margins

J. Bauer

(904) 644-9646

\$180,000

This research quantifies the transformation rates and mechanisms of exchange between dissolved, colloidal small particle and large particle size classes of organic carbon in ocean margins. The approach is to combine the particle transformation rate information obtained using the thorium isotopes (^{232}Th , ^{230}Th , ^{234}Th) with information on particle source and age using carbon isotopic information ($\delta^{13}\text{C}$ and $\delta^{14}\text{C}$). The colloidal phase, traditionally collected along with the filtrate, is being sampled in situ using cross-flow filtration techniques. High temperature combustion techniques are being used to measure organic carbon in dissolved and colloidal forms. Field sampling methods involve the collection of particulate matter using filters (33 μm) as well as the direct separation of colloidal material (>0.2 μm and >5,000 NMW) via cross-flow filtration and the collection of the dissolved filtrate.

The nature of this research requires the coordinated use of innovative sampling and sensitive analytical techniques that have only recently been developed. Therefore, five principal investigators are focusing their efforts on a limited number of samples from continental shelf waters off the northeast U.S. Researchers plan three cruises from Woods Hole out to oceanic waters. (RPIS 10679)

584. Numerical Studies of Bottom Boundary Layer Processes Along the Continental Margin

G.L. Weatherly

(904) 644-2875

\$59,000

The basic assumption of this work is that the bottom boundary layer (BBL) plays an important role in transporting excess carbon from the Continental Shelf to the ocean interior. This assumption is based in large part from what has been surmised and learned in the Shelf Edge Exchange Processes I program. For example, the 1990 Dynamics of Continental Margins: A report to DOE states that owing to the prevailing currents, ... the BBL ... provides the most obvious pathway for the fluid to move off the shelf. The importance of BBL is not limited to transporting fluid across the shelf to the shelf break. BBL also appears to be important in transporting carbon down the continental slope. As the fluid advects down the slope in the BBL, it is leaked out into the ocean interior.

The leaky BBL process is attractive in that it accounts for the sediment trap data of others, and it seems quite plausible. However, dynamically it is not well understood. BBL on the continental slope is generally assumed to be like that on the deep ocean bottom. That is, it is a turbulent Ekman layer, and the downslope transport in the BBL fluid to the ocean interior is thought to be associated with buoyancy forces, changes in the bottom slope, variations in currents, and changes in the density field. However, their relative roles are not known. Moreover, the assumption that BBLs on continental margins are basically similar to BBLs in the deep ocean is now not as tenable as before.

Proper assessment of the role of BBL in the transport of organic carbon will require understanding BBL dynamics on continental margins. It has become apparent recently that BBLs on continental margins are fundamentally different from those on the abyssal ocean bottom. Basically, the buoyancy force resulting from up or down slope BBL Ekman transport has profound influence on BBLs on continental margins; it has a negligible effect on BBLs on abyssal plains.

Studies show that buoyancy forces on continental margins "shut down" BBL for several days. That is, the bottom stress and, more importantly to the scope of the Ocean Margins Program, the BBL transport becomes effectively zero after a few days. (RPIS 10667)

Geotech Inc.
Grand Junction, CO 81502

585. Extension of ^{210}Pb Geochronology with Inverse Numerical Techniques

J. Carroll

(303) 248-6058

\$48,000

A novel procedure for interpreting complex sediment ^{210}Pb profiles is designed to improve the resolution and streamline the determination of ^{210}Pb accumulation rates. These improvements will directly benefit the Ocean Margins Program by providing better information on spatial and temporal patterns of ocean sedimentation information that is needed to determine the dynamics of carbon burial on continental shelves.

The procedure combines inverse numerical techniques with predictive models to separate source variations from sediment accumulation variations in nonuniform isotope profiles. The technique is powerful because it does not require knowledge of the exact causes of the observed isotope variability.

This new procedure shows promise. However, further research is needed to determine its practical capabilities and limitations. To this end, this project strives to continue development of the numerical algorithms, test the accuracy of the model using synthetic ^{210}Pb sediment profiles, and perform additional tests using presently available isotope profiles. (RPIS 5685)

K.C. Research Corporation
Littleton, CO 80127

586. A Marine Boundary Layer Water Vapor Flux Sensor

T.A. Cerni

(303) 979-6376

\$49,823

Calibration of advanced DOE oceanic and atmospheric chemistry models requires synoptic scale global data sets of atmospheric-oceanic fluxes of water vapor. However, current instrumentation and sensing techniques appear incapable of yielding accurate data over an extended period of time in the harsh marine boundary layer. The major problem lies in the area of fast response humidity sensors that will survive the marine environment. This project explores an innovative laser hygrometer that will be combined with either a sonic anemometer or a laser Doppler anemometer to provide an all-solid-state sensor system with no moving parts for measuring marine boundary layer water vapor flux. The key elements of the laser hygrometer are similar to those used in undersea fiber optic cables designed for 10 years of autonomous operation. Use of a noncontact humidity-sensing technique means that the sapphire windows are the only sensor elements that require contact with the harsh marine environment. Response times of 10 to 20 Hz are typical, and the response time is fundamentally limited only by the speed at which the ambient wind flushes the

small sample volume. The humidity measurement technique is sufficiently stable and reliable to allow a single sensor to be used for measurements of both water vapor flux and steady-state humidity. The Phase I workplan includes laboratory and atmospheric testing of a proof-of-concept water vapor flux sensor, marine testing for investigation of potential optical window problems, and the drafting of a Phase II sensor design and Phase II workplan.

This new measurement capability could make a significant contribution to DOE's overall program goals of achieving a better understanding of the ocean's role in global climate change and the environmental consequences of energy use. While being responsive to DOE scientific program interests, this line of research could also result in a new generation of practical, cost effective, ultrasensitive, very rugged hygrometers for the industrial sector. Industrial applications will benefit the Nation's economic competitiveness in manufacturing systems. (SBIR)

Louisiana Universities Marine Consortium
Chauvin, LA 70344

587. Assimilation and Transfer of Carbon in Oligotrophic and Eutrophic Coastal Water Columns

M. Dagg

(504) 851-2800

\$320,000

The amount of carbon discharged into the atmosphere from energy and industrial sources during the past 200 years is greater than can be accounted for by estimates of what remains in the atmosphere plus what has been absorbed by the terrestrial and oceanic systems. Estimates of carbon apportioning between the land and oceans are uncertain, but one possible location for some of this "missing" carbon is the open ocean below the thermocline. Another suggested location is the coastal ocean, where approximately 50 percent of the ocean's biological productivity occurs. As part of a DOE/OHER Ocean Margins Program, researchers are examining biological processes in the water column that assimilate, transform, and recycle dissolved and particulate organic carbon in coastal ocean waters.

In this project, researchers focus on the water column processes. Although variable, the proportion of production that sinks from the euphotic zone typically indicates that a major fraction of fixed carbon is recycled within the euphotic zone. This work aims to clarify understanding of the processes that control these water column fates and to predict the subsequent flux out of the euphotic zone based on the understanding of these water column processes. (RPIS 10666)

University of Maine Walpole, ME 04573

Department of Oceanography

588. Adsorption Control of Organic Carbon Burial in Ocean Margin Sediments

L.M. Mayer

(207) 563-3146

\$129,000

Organic carbon (OC) burial on continental margins is one of the more important terms to understand in any program addressing overall carbon dynamics in this oceanic regime. The relatively high sedimentary OC concentrations coupled with relatively high sedimentation rates make this burial term an important one in overall oceanic carbon budget. This research tests a new paradigm for the control of OC concentrations, decay rates, and burial fluxes in margin sediments.

OC concentrations have long been known to correlate inversely with grain size in marine sediments especially in Continental Shelf regions. This relationship has received little explanation or application to a variety of problems regarding sedimentary organic matter. Some data are being examined that provide a clue to a much more coherent relationship between grain size and OC concentrations than has been considered. The implications of this work is assisting in (1) rationalizing OC burial fluxes on continental margins, (2) delineating the amount of metabolizable OC on certain time scales, and (3) providing some mechanistic understanding of the protection of sedimentary organic matter on millennial time scales by adsorption. (RPIS 10686)

Marine Biological Laboratory Woods Hole, MA 02543

The Ecosystems Center

589. Origins and Fates of Dissolved Organic Matter Along the New England Continental Margin

B. Fry

(508) 548-3705

\$168,000

Current concepts of the oceanic carbon cycle are being revolutionized. New measurements show that the largest organic pool, dissolved organic matter (DOM), has an active cycle of production and consumption in the upper ocean. Because the DOM pool is roughly twice the size of the current atmospheric carbon pool and is connected to it via phytoplankton carbon fixation in the sea, it is possible that even relatively small changes in DOM pool sizes can be important modulators of carbon circulation in a global context.

This research documents the distribution and metabolism of DOM in a highly productive continental margin area, the shelf and slope system located near Georges Bank. Because considerable controversy still exists about the basic measurement techniques involved in studies of DOM, a first-

year study is being devoted to completing current development of two new, independent methods for combined measurement of dissolved organic carbon and dissolved organic nitrogen. Building on this new technology, researchers will survey DOM distributions along the New England continental margin, using a multiple tracer approach to locate important sites of DOM production and consumption.

It is likely that sites of downwelling may be important oceanic pumps leading to carbon storage in deep water DOM. This idea depends on low temperature retarding decomposition of surface DOM that has been advected to deep water. Using experimental mesocosms, researchers will test effects of temperature, nutrients, and presence of protozoan grazers on DOM metabolism. DOM production during phytoplankton blooms will also be studied in field settings. (RPIS 10682)

Monterey Bay Aquarium Pacific Grove, CA 93950

Research Institute

590. A New Instrument for Measuring Sinking Rates of Marine Particulates In Situ

C.H. Pilskaln

(408) 647-3719

\$99,000

This work develops the first semi-automated instrument for measuring the sinking rates of naturally occurring particles in the sea. This new instrument is a modification of a particle-sizing and particle-counting device called the Marine Aggregate Measurement System (MAMS) now in operation at the Monterey Bay Aquarium Research Institute (MBARI). MAMS obtains high quality video images that are subsequently analyzed with special software packages, enabling the rapid analysis of particles from transects through the water column. MAMS is presently mounted on the MBARI remotely operated vehicle (ROV), which allows real-time control of the data-gathering operation. Dye injection ports are being added to the existing instrument, and protocols for measuring the sinking rates of particles >0.5 mm in surface waters to depths below the mixed layer are being developed. Initial tests of the instrument are obtaining some sinking measurements for different types of particles at various depths, including at those depths known to be advecting shelf materials offshore. A prototype instrument is being developed, and field tests of the instrument are being made in a particle-rich environment of the shelf and canyon of Monterey Bay, where ROV and MAMS are presently operational. As the sinking rate capability of the instrument is developed, researchers will be collaborating with the Ocean Margins Program community of investigators to ascertain which modifications would make the instrument most useful for future work by the research community. The work focuses on developing a high precision instrument that has maximum inherent flexibility. (RPIS 10691)

National Academy of Sciences
Washington, DC 20418

Ocean Studies Board

591. Support of the Ocean Studies Board

M.H.M. Katsouras
(202) 334-2714

\$24,000

The Ocean Studies Board advises the DOE and the scientific community on directions that will lead to an improved understanding of carbon in the ocean and its exchange with the atmosphere. Three important issues are (1) new sensors for oceanic carbon and other elements and compounds in the marine environment, (2) ocean carbon measurements and data, and (3) carbon fluxes across air-sea and sediment-water surfaces.

The committee is studying new measurement technologies for the ocean—primarily sensors of chemical and biological properties—enlisting the aid of analytical chemists to help its oceanographers recommend new technologies for the measurement of carbon dioxide and other biologically important elements and compounds. The committee will publish a report to discuss its findings and will also consider publishing a report on atmospheric CO₂ standards.

The committee will convene a workshop on CO₂ exchange across the air-sea interface. The workshop will consider how various chemical and isotopic tracers may be used to explain CO₂ uptake by the oceans. The workshop would bring together participants from the fields of atmospheric and ocean sciences, chemical and mechanical engineering, and related fields.

Management of oceanic carbon data is also being addressed. Data are collected by agencies and international research programs but are not accessible in a central location. Such access is desirable to make the best data available within a reasonable period of time. (RPIS 10366)

Polar Research Board

592. Polar Research Board

S.B. Abbott
(202) 334-3479

\$35,000

The Polar Research Board is monitoring the status and needs of polar sciences. The Board is also assisting U.S. Government agencies in the development and maintenance of strong programs of polar research that are responsive to scientific and technical opportunities and national interests in the Arctic and Antarctic. The core program includes the studies conducted by the Board, the activities of two committees one on permafrost (including geophysical, climatological, and engineering concerns), the other on glaciology (including research on snow, floating ice, and glaciers) and service as the U.S. National Committee for the Scientific Committee on Antarctic Research of the International Council of Scientific Unions and the U.S. Committee for the International Arctic Science Committee (IASC). IASC is a recently established nongovernmental sci-

ence body designed to facilitate cooperation in and coordination of all fields of arctic science. The Polar Research Board provides a forum for the exchange of ideas; conducts studies; holds workshops, symposia, conferences, and meetings; establishes a dialog between representatives of U.S. Government agencies and the polar scientific community on selected topics of national importance; and provides the means for U.S. participation in international polar science activities. Each year, the proposal for continuing support summarizes all activities and reports prepared as a result of the Board's deliberations. The Board also prepares a periodic report summarizing such activities and plans for the future. In addition, the Board prepares an annual catalog of scientific research programs supported by U.S. Government agencies and conducted in the Antarctic. The reports are useful to the scientific community, legislators, representatives of the U.S. Government agencies, environmental and other nonprofit organizations, and industry. (RPIS 10216)

National Science Foundation
Washington, DC 20550

593. University National Oceanographic Laboratory System

R. West
(202) 357-7837

\$11,000

University National Oceanographic Laboratory System (UNOLS), an association of 17 academic institutions, was established in 1971 by the National Science Foundation, as a coordinating and planning mechanism for oceanographic facilities operated by those institutions. Thirty-one other academic institutions participate in UNOLS as associate members. The UNOLS office is the focal point for planning, coordinating, and reporting of all UNOLS activities and is supported by six Federal agencies. It provides administrative staff services and prepares and disseminates ship schedules, user requirements, analyses of annual ship use, committee reports, new marine regulations, and other related information. Support for travel expenses of UNOLS advisory council members, committees, and consultants is also furnished by the UNOLS office. This service provides the maximum degree of cooperation among agencies. (RPIS 9880)

University of North Carolina at Chapel Hill
Chapel Hill, NC 27599

Department of Geology

- 594. Carbon Cycling on the Continental Margin: Evidence from Sediment ^{14}C and Nutrient Elements**
L.K. Benninger
(919) 962-0699 **\$149,000**

This research characterizes carbon and nutrient storage and turnover in sedimentary reservoirs of the continental margin through measurements on the solid phases by—

- Establishing a radiocarbon capability in the geochemistry-geochronology laboratories at the University of North Carolina at Chapel Hill to measure ^{14}C in shelf, slope, and rise sediments.
- Collecting sediment cores for ^{14}C and nutrient analyses along margin transects located north and south of Cape Hatteras, North Carolina.
- Performing and interpreting chemical and radiochemical analyses to yield rates of carbon and nutrient storage and remineralization in continental margin sedimentary environments. (RPIS 10669)

North Carolina State University
Raleigh, NC 27695

Department of Marine, Earth, and Atmospheric Science

- 595. A Study of Sediment Motions and Bottom Boundary Layer Dynamics Over the Mid-Atlantic Bight Shelf and Upper Slope**
L.J. Pietrafesa
(919) 515-3717 **\$228,000**

The interaction of the bottom sediments and the flow field of the shelf and slope of the Mid-Atlantic Bight (MAB) is being studied. The study encompasses the entire suite of fluid mechanical processes present in the separate areas of the shelf/slope muds and shelf/slope sands during winter and summer. In the winter, the Shelf/Slope Front (SSF) in MAB intersects the bottom in the vicinity of the shelf break to mid-shelf, while the water column coastward of SSF is in a relatively unstratified condition. This forms a partial barrier to the offshore internal wave field (IWF) so that its energy could disappear or be reflected from the base of the front. Higher sea states and more energetic wind-induced currents are also present during the winter. Alternatively, during the summer, the shelf becomes strongly stratified; the frequency and intensity of wind events is reduced; the gravity wave field is much reduced; and IWFs are likely to propagate across the entire shelf.

This work (1) investigates temporal and spatial variability of the bottom, benthic boundary layer (BBL); (2) identifies and quantifies the forcing functions manifested in BBL; (3) determines and quantifies the dissipation of energy in BBL;

(4) assesses the transport of sediments and mixing in BBL; and (5) determines and quantifies the role of BBL in the carbon budget, in particular the potential of bottom sediments to be either sources or sinks of carbon. (RPIS 10678)

Ocean Optics, Inc.
Dunedin, FL 34698

- 596. Inherently Calibrated Fiber Optic Sensors for Measuring Seawater pH**
M.J. Morris
(813) 733-0782 **\$499,416 (2-year funding)**

Oceanic uptake of CO_2 reduces the atmospheric burden of this greenhouse gas. Quantification of this process will require highly accurate and precise sensors capable of unattended operation at sea. Phase I demonstrated the feasibility of an optical pH sensor that is inherently calibrated and therefore capable of unattended operation. Immobilized dyes in transparent films are interrogated by a fiber optic spectrometer. Absorbance spectra of the dye can be related to the pH of surrounding media with chemical and optical constants alone. These constants can be independently determined to high levels of precision and can be used to calculate the pH of the film to 0.001 pH units. Because of inherent calibration, deployment for long time periods in seawater and fouling of the film were found not to affect the accuracy of pH measurements. A proof-of-principle diode array spectrometer was able to couple to the sensor with optical fibers and collect data for in situ pH measurements. Phase II includes the design, building, deployment, and testing of a sensor and spectrometer system that will collect pH data from several depths in a continuous and unattended mode. The spectrometer uses hybrid dual beam optics and software strategies to correct for source and detector sensitivity and shifts in background absorbance of the sensor. The array is tested at sea with sensors reaching 1,000-m water depth.

The inherently calibrated pH sensor and fiber optic spectrometer allows researchers to collect the highly precise data necessary for characterizing the ocean's response to anthropogenic CO_2 inputs. Additional applications include monitoring of acidic precipitation with instruments deployed on land. Phase III activities lead to commercial production of an inherently calibrated pH monitor for wastewater streams. Because the sensor can be autoclaved, bioprocess control uses are expected. (SBIR)

- 597. A Multi-temperature Optical System for In Situ Measurement of the Flux and Sinking Speed of Marine Snow Aggregates**
R.A. Walters
(813) 733-2447 **\$497,000 (2-year funding)**

Much of the anthropogenic CO_2 released to the atmosphere may be transported in the form of particles from the ocean surface to deep water where it is effectively sequestered. Quantifying the

vertical flux of particulate carbon in the oceans is therefore essential in order to predict the consequences of continued CO₂ emissions. Existing methods for measuring particle fluxes are prone to errors due to hydrodynamic effects on collector efficiency and compromise of collected samples by biological activity. This project is developing an optical sensor based on the insect eye, which is capable of detecting particles in a remote and noninvasive manner. The multiaperture sensor (MAS) is highly redundant and can tolerate the loss of sensing elements, biofouling of optical surfaces, and the rigors of oceanographic deployment. Phase I demonstrated the ability of MAS to detect and track marine snow aggregates, forams, and other particles larger than 100 microns. Variance signals from the elements were correlated with size and speed of the particles, suggesting that mass flux might be sensed directly. Phase II is developing advanced data processing software including triangulation, variance and covariance, and neural net training. An autonomous MAS system is deployed at sea on a neutrally buoyant platform.

MAS sensors expand the range of particle sizes that can be analyzed with optical techniques and enhance the process control capabilities of fiber optic spectrometers. The sensors may also find use in packaging monitoring, the study of aerosols, zooplankton behavior, or any application where particle motion is of interest. (SBIR)

University of Oregon
Eugene, OR 97403

Department of Biology

- 598. Phytoplankton Excretion Revisited: Healthy Cells May Not Do It, But How Many Cells Are Healthy?**
A.M. Wood
(503) 346-2862 \$89,000

This research is developing molecular tools for determining the health of marine phytoplankton on an individual cell basis. Because the definition of "healthy" phytoplankton cells is elusive, researchers are developing markers for several different metabolic processes indicative of physiological state: photosynthetic activity, esterase activity, membrane permeability, and mitochondrial activity. One underlying motivation is to develop methods that allow evaluation of the hypothesis that, while healthy cells release very little dissolved organic carbon (DOC), many phytoplankton communities are composed of "unhealthy" or physiologically stressed cells that release a large proportion of total photosynthate directly into the pool of labile DOC. This is proposed to be especially true in continental shelf and coastal environments in which zones of productivity are patchy and phytoplankton populations adapted to one regime can be easily transported into waters that differ in salinity, nutrient supply, or turbidity.

The significance of the work, however, extends beyond this immediate goal. Presently, relatively few methods allow researchers to estimate the physiological state of phytoplankton

cells. When population sizes of phytoplankton in the water column are evaluated, or fecal pellets, particulate aggregate, or other material are examined, the activity of the cells is generally unknown, except as the average cell-specific activity is estimated from bulk measurements. This approach effectively hides any differences in the relative contribution of different taxa or individuals to overall productivity, even though most flux processes are sensitive to physiological and taxonomically determined differences among members of the community. (RPIS 10664)

Oregon State University/University of Oregon

Corvallis, OR 97331/Charleston, OR 97420

College of Oceanography/Oregon Institute of Marine Biology

- 599. Controls on Marine Carbon Fluxes via Phytoplankton: Microzooplankton Interactions in Continental Shelf Waters**

B.F. Sherr

L.P. Shapiro

(503) 737-4369/(503) 888-2581 \$77,000/\$85,000

A comprehensive study of the trophic interactions between phytoplankton and their dominant grazers, phagotrophic protists, in shelf waters is being conducted in coordination between the two laboratories. Outside of spring blooms and occasional upwelling-associated blooms, most of the marine photosynthetic biomass is packaged in cells too small to be effectively grazed by metazooplankton. Even when diatoms are the dominant phytoplankters, copepods and other metazooplankton may show a preference for grazing on the protistan predators of smaller phytoplankton. Thus, in the most recent concepts of the structure of pelagic food webs, the phytoplankton → protist trophic step is the major route by which phytoplankton-fixed carbon is processed. This key interaction determines the relationship between phytoplankton rate processes and standing stocks and is a major controlling factor in determining the proportion of primary production available for metazoan food webs or export to the benthos.

This research investigates the effects of protistan grazing on cell-specific phytoplankton growth rates and rates of photosynthesis, quantifies the proportion of phytoplankton biomass in the water column that is utilized in the protistan food web, and determines the efficiency of carbon transfer in the major trophic pathway of phytoplankton → protist. The results will provide essential information about the processes by which carbon is fluxed through shelf ecosystems.

The project is also comparing results of published methods and developing and testing improved methods for estimation of protistan grazing rates and phytoplankton cell reproduction rates. (RPIS 10663/RPIS 10665)

Sea Tech, Inc.
Corvallis, OR 97339

**600. Calibration of In Situ Optical Devices
Using a Pure Water Standard**

R. Bartz

(503) 757-9716

\$268,171 (2-year funding)

During Phase II, a variable pathlength spectral attenuation meter (VPSAM) is being developed and constructed for oceanographic use in calibrating spectral attenuation meters. A laboratory VPSAM determines the attenuation coefficient by measuring the slope of the relation of the log of the transmission and distance. In this manner, almost all optical properties of the sender and receiver are divided out. Only the collimation of the light affects the results. A major effort thus is being made to collimate the light as much as possible by using long focal-length optics. A filter wheel allows the measurement of spectral variations. An optical feedback scheme compensates for any variations in light intensity. The commercial development of such a device, together with further development of the revers osmosis clean water tank carried out during Phase I, will allow spectral attenuation meters to be calibrated over decades so as to study global changes over long periods of time.

Together with the optically pure water tank developed during Phase I, the commercial availability of VPSAM will allow the calibration of in situ devices over decadal time periods. This calibration is required by researchers at government, university, and private industry laboratories involved in studies of global climate change and its influence on the biosphere. (SBIR)

**601. Development of a Spectral Attenuation Meter
and a Spectral Back Scattering Meter**

R. Bartz

(503) 757-9716

\$499,830 (2-year funding)

This project involves the construction and evaluation of prototype in situ spectral attenuation and back scattering meters. These instruments, together with spectral absorption, are needed for researchers to understand the radiative transfer properties linking the remotely sensed ocean color spectra to the state of the oceanic biosphere. Such studies are crucial to the global monitoring involved in documenting those processes related to the greenhouse effect and ozone depletion. No such in situ instruments are now commercially available. The spectral attenuation meter design is based on the laboratory model developed during Phase I. In this design, light is collected from a tungsten bulb and fed into a holographic monochromator. The output is monitored by a reference detector with a pinhole in it. The light is then collimated and transmitted through the water path, after which it is focused on a small area detector. Much of the electronics needed has already been designed. Major effort is being expended on perfecting the light source and monochromator, packaging the instrument for underwater use, and performing calibration and field validation. Calibration is

carried out by means of a variable pathlength spectral attenuation meter being developed under a separate project. The spectral back scattering device is based on a fluorometer and the prototype single wavelength device developed during Phase I. Improved electronics and an optical bridge scheme increase sensitivity by a factor of 10. The sensor detects light scattered between 102.5° and 167.5° with a gaussian structure about 135°. The central angle can be varied. A filter wheel will be part of the design.

Prototype spectral attenuation and back scattering meters for use in oceanographic work are being designed, constructed, and tested to facilitate their commercial availability. The devices could find widespread use among researchers at government, university, and private industry laboratories involved in studies of global climatic change and its influence on the biosphere as well as studies involving remote sensing, radiative transfer, and oceanic biology. (SBIR)

Skidaway Institute of Oceanography
Savannah, GA 31416

**602. Burial, Remineralization, and Utilization of
Organic Matter at the Seafloor Under a
Strong Western Boundary Current**

R.A. Jahnke

(912) 598-2491

\$231,000

Researchers are studying the burial, remineralization, and microbial utilization by micro-organisms of organic matter at five sites on the North Carolina slope and rise. At each site, benthic flux rates are being determined by in situ chamber measurements, pore water and sediment samples are being recovered for chemical analyses, and microbial production rates are being estimated. Sedimentary excess ^{210}Pb and ^{14}C activities are being determined to assess rates of sediment mixing and accumulation. At each site, total input, recycling, and burial of the major biogenic elements are being estimated. Because bottom water O_2 concentrations in the Atlantic are approximately twice those in the North Pacific, the sensitivity of organic carbon burial to bottom water chemistry can be directly determined by comparing the results of new measurements with those already obtained for the North Pacific. In addition, the North Carolina continental rise should be a depocenter for materials transported by the Gulf Stream. As such, evaluation of carbon fluxes in this area will help estimate the importance of biological productivity and export in the western boundary current system to the organic carbon cycle of the deep North Atlantic. (RPIS 10661)

603. The Impact of Proto- and Metazooplankton on the Fate of Organic Carbon in Continental Ocean Margins

G. Paffenhofer

(912) 598-2489

\$283,000

New primary production (due to uptake of nitrate-N) in western boundary currents originates in waters that carry large amounts of nutrients and are displaced into the euphotic zone. Most new primary production off the southeastern U.S. takes place in Gulf Stream eddies along the outer shelf/shelfbreak that, on average, pass by at a rate of one per week and have a large core of cold, nutrient-rich water. These eddies from near 28° S grow as they travel north and may dissipate near or north of the Charleston Bump. The fate of the large amounts of primary production in these eddies is largely unknown.

This work is contributing to the understanding of the fate of that primary production by determining the amounts of phytoplankton removed by proto- and metazooplankton grazers. Specially, the following three hypotheses are being tested:

(1) If the seed population of zooplankton in an eddy is dominated by gelatinous travel (Tunicata), as much as 50 percent of the new primary production may be ingested by these rapidly growing populations; the nonassimilated matter most likely sinks rapidly (fecal pellets of salps).

(2) If phagotrophic protzoa constitute a significant part of the seed population in a developing eddy, a considerable portion of the primary production is consumed by fast-growing populations; because of the small size of their fecal products, however, the nonassimilated carbon remains in the water column.

(3) If most of the seed population of zooplankton of the eddy consists of copepods, only a small part of that eddy's primary production between Cape Florida and the Charleston Bump is consumed. This is so because copepod weight-specific feeding rates are lower and their growth rates are slower than those of protozoa and salps. Thus, most of the primary production would be transformed after being displaced toward or into the open ocean. (RPIS 10662)

University of Southern Mississippi

Stennis Space Center, MS 39529

Center for Marine Science

604. Development of a Multisensor In Situ Fiber Optic Fluorometer

S.E. Lohrenz

(601) 688-1176

\$95,000

Goals of DOE's Ocean Margins Program include quantification of primary production and flux of phytoplankton biomass on the Continental Shelf and determination of controlling mechanisms. To accomplish these objectives, high resolution time-series observations of the distribution and abundance of particulate pigment biomass are required. Discrete shipboard

sampling inadequately resolves variations in particulate pigment biomass related to changing environmental conditions. Many important physical variables have time scales ranging from minutes to hours. Hence, the coarse temporal resolution provided by discrete sampling techniques may lead to aliasing. Furthermore, shipboard studies have limited duration and may miss episodic (e.g., weather related) as well as seasonal scale events.

Researchers are developing and evaluating a multisensor in situ fiber optic fluorometer. The instrument is designed to sample and store in vivo strobe-stimulated fluorescence data at multiple depths and high frequencies (1 Hz). This information may be used for estimating the distribution and abundance of particulate pigment biomass in support of models of water column primary production as a complement to remotely sensed ocean color estimates of pigment biomass. The instrument is unique in that it uses fiber optic technology to increase vertical resolution. Although it is theoretically possible to accomplish this task using a large number of commercially available fluorometers, this design provides a less expensive approach. (RPIS 10689)

State University of New York at Stony Brook

Stony Brook, NY 11794

Marine Sciences Research Center

605. Multiple Tracer Measurement of the Coupling Between Benthic C Fluxes and Bioturbation Activity During the 'Spring Bloom'

R. C. Aller

(516) 632-8746

\$160,000

A large proportion of the total annual biogenic material flux to the seafloor can occur over relatively short time periods such as the spring or fall 'blooms' in temperate marine environments. The fate of such pulses of material is determined by balances between the magnitude and duration of inputs, the physical sedimentation regime, temperature control of metabolic reaction rates, and bioturbation activities of benthic communities. Bioturbation plays a particularly central role in determining relative aerobic and anaerobic reaction rates during initial burial. The pathways of remineralization of organic matter, recycling patterns, and burial of biogenic debris during bloom periods is relatively poorly documented but is central to understanding time scales, and extent of elemental cycling and storage. Time varying inputs of material to the seafloor, bioturbation rates, and reaction rates must be accurately quantified to formulate and evaluate conceptual models of benthic processes and to predict fluxes. The present study compares multiple tracers of reactive C supply, particle flux, particle reworking, decomposition rates, carbonate formation, and dissolution, during a spring bloom period at a single field site. The study's purposes are to both examine fundamental benthic recycling processes during the bloom and to evaluate the coherence between different tracer estimates of rates and

boundary conditions at the seafloor for general use. The project is utilizing simultaneously, high temporal resolution sampling of natural radiochemical tracers (^{234}Th , ^7Be), organic geochemical tracers (chloropigments), luminophores (fluorescent particles), and the dynamics of small carbonate-bearing benthos (juvenile bivalves, forams) to quantify particle flux, reworking, and net benthic carbonate dissolution. Oxygen, CO_2 , ammonium, and manganese solute fluxes are measured together with ammonification rates to help quantify decomposition and redox reaction balances during the same period. Nonsteady state diagenetic models are used to quantify fluxes and transport-reaction coupling in each case. (RPIS 10709)

Texas A&M University
Galveston, TX 77553

Department of Marine Science

- 606. The Production of Colloids in the Benthic Boundary Layer and Particle-Particle Interactions**
P. Santschi
(409) 740-4476 \$836,000

The last several years have seen the subject of oceanic colloids transformed from one of relative obscurity to one now occupying a central place in the frontline of chemical oceanography research. In spite of the progress already made, a major gap exists in the understanding of the mechanisms resulting in the generation of colloidal material. These researchers hypothesize that the benthic boundary layer (BBL) is a critical, if not dominant, source of colloids in continental and shelf regions. The work here is clarifying understanding of (1) the mechanisms of colloid generation at BBL, (2) the distribution of colloidal material throughout various material pools, and (3) the rates of interaction of colloidal organic carbon between those pools. The goals are being achieved through a series of coupled field and laboratory studies and process-oriented modeling. Field experiments include investigations of isotopic (e.g., Th, Pb, Ra radioisotopes, ^{14}C , and ^{13}C), elemental (e.g., C_{org} , CaCO_3 , SiAl, Fe, Mn, selected trace elements, and rare Earth elements), biomarker (e.g., ligninphenols, pigments) composition of colloids; and suspended, sinking, and freshly deposited particles to determine age and source functions. These measurements are being carried out in concert with those of shear stress by alabaster dissolution on the Texas/Louisiana shelf and slope. Laboratory experiments are determining the flux of colloids out of surface sediments (resuspension) as a function of interfacial shear stress. (RPIS 10668)

Texas A&M University
College Station, TX 77843

Department of Oceanography

- 607. Optical Assessment of Large Marine Particles: Development of an Imaging and Analysis System for Quantifying Large Particle Distributions and Fluxes**
I.D. Walsh
(409) 845-7521 \$191,000

The central goal of DOE's Ocean Margins Program (OMP) is to determine whether continental shelves are quantitatively significant in removing carbon dioxide from the atmosphere and isolating it via burial in sediments or exporting it to the open ocean. A major component of OMP is to measure carbon flux on the shelf and across the shelf to the slope and open ocean. This research is developing an optical instrument package and the analytical techniques to measure precisely a wide spectrum of the large aggregate population of particles in the shelf/slope environment. This particle population, encompassing the "marine snow" size particles (diameters $>0.5\text{ mm}$), is thought to be the major pathway of material flux in the ocean and increasingly has been found to be an important site for biogeochemical processes. (RPIS 10694)

Woods Hole Oceanographic Institution
Woods Hole, MA 02543

Biology Department

- 608. Moored Instrument for Time-Series Studies of Primary Production and Other Microbial Rate Processes**
C.D. Taylor
(508) 548-1400 \$192,000

This project is building and testing a time-series submersible incubation device (TS-SID) capable of the autonomous in situ measurement of phytoplankton production and other rate processes for a period of up to at least 3 months. The instrument is conceptually based on a recently constructed submersible incubation device (SID). TS-SID will have the ability to periodically incubate samples in the presence of an appropriate tracer and to store chemically fixed subsamples for later analysis. The instrument will be able to collect a total of 88 incubated samples. TS-SID is designed to simulate natural environment accurately and to avoid trace metal contamination and physical damage to cells. Devices for biofouling control of internal and external surfaces will be incorporated into the instrument. After the time-series capabilities of the instrument are successfully evaluated by medium-term coastal time-series studies (up to 1 month), longer-term coastal time-series studies (2–3 months) will be conducted to evaluate the biofouling prevention measures that have been used with the instrument. (RPIS 10660)

Department of Chemistry

609. Fiber Optic Chemical Sensors for Characterizing the Carbon Cycle in Ocean Margin Regions*M. D. DeGrandpre*

(508) 457-2000

\$90,000

Oceanographers lack detailed information about the biogeochemical cycling of carbon in ocean margin regions. High density temporal and spatial measurements of dissolved carbon species would help quantify the ocean margins' influence on atmospheric CO_2 and would improve constraints on models used to predict global climate. Surface ocean pCO_2 is an important component of the carbon cycle because it directly influences CO_2 gas exchange between the ocean and atmosphere. Long-term characterization of surface ocean pCO_2 requires a commitment to the development of new measurement technology that can operate remotely in situ and that can be implemented at relatively low cost. Fiber optic chemical sensors (FOCS), developed originally for biomedical and industrial applications, have not matured to a level where reliable long-term measurements of pCO_2 are possible. Previous fiber optic sensors for pCO_2 have had poor long-term stability because of reagent degradation and leaching. Recent innovations in the design of FOCS allow the reagent to be periodically or continuously renewed. A pCO_2 fiber optic sensor has been developed based on the renewable reagent design. With the new sensor design, researchers are developing a pCO_2 measurement system capable of taking remote, unattended measurements for extended periods (i.e., months). In addition, the knowledge gained from the development of the pCO_2 sensor is being extended to the development of sensors for pH, TCO_2 , and possibly pO_2 to more fully characterize the carbon cycle. The results of long-term studies will be used to evaluate the feasibility of widespread remote deployment of the pCO_2 sensor. (RPIS 10687)

610. Transformation Rates and Fate of Dissolved, Colloidal, and Particulate Forms of Organic Carbon in Ocean Margins*E.R.M. Druffel*

(508) 457-2000

\$176,000

This research quantifies the transformation rates and mechanisms of exchange between dissolved, colloidal small particle and large particle size classes of organic carbon in ocean margins. The approach is to combine the particle transformation rate information obtained using the thorium isotopes (^{234}Th , ^{228}Th , ^{230}Th) with information on particle source and age using carbon isotopic information (^{14}C and ^{13}C). The colloidal phase, traditionally collected along with the filtrate, is being sampled in situ using cross-flow filtration techniques. High temperature combustion techniques are being used to measure organic carbon in dissolved and colloidal forms. Field sampling methods involve the collection of particulate matter using filters (33 m) as well as the direct separation of colloidal material (>0.2 m and >5,000 NMW)

The nature of this program requires the coordinated use of innovative sampling and sensitive analytical techniques that have only recently been developed. Therefore, five principal investigators are focusing their efforts on a limited number of samples from continental shelf waters off the northwest U.S. Three cruises from Woods Hole out to oceanic waters are planned. (RPIS 10676)

611. Characterization of Macromolecular Components of Particulate, Colloidal, and Dissolved Organic Matter at the Sediment-Water Interface: Implications for Organic Matter Degradation Versus Preservation During Early Diagenesis in Shelf Sediments*D.J. Repeta*

(508) 457-2000

\$143,000

Benthic remineralization of organic matter plays a major role in determining the fate of carbon in coastal ecosystems. The high rate but dynamic nature of productivity over the shelf results in a partial decoupling of production and remineralization processes, such that a large fraction of the organic matter produced by phytoplankton escapes remineralization in the water column and sinks to the sediment-water interface. Very rapid remineralization of labile organic matter at the sediment-water interface may return nutrients and bioactive elements to the water column and fuel further production. Resistant organic matter may persist in shelf sediments or be advected from the shelf and deposited on the adjacent continental slope.

Current understanding of early diagenesis is limited by an inability to analyze a significant (>50 percent) fraction of TOC in detritus and surface sediments. There is no molecular level explanation of why some fraction of organic carbon is reactive while a compositionally similar fraction of organic matter is nonreactive. Consequently, diagenetic models cannot be critically evaluated and the fate of primary production on the continental margins cannot be adequately determined. This work is developing and applying analytical techniques that are broadly applicable to studying a large fraction of the total carbon in particulate, dissolved, and colloidal organic matter (POM, DOM, and COM).

This research has four objectives: (1) to develop instrumental techniques for the quantitative analysis of complex biopolymers; (2) to compile a comprehensive inventory of major biochemicals in POM, DOM, and COM recovered from the water column, sediment-water interface, and surficial sediments; (3) to quantitatively assess the contribution of continentally derived weathered kerogens to margin sediment; and (4) to evaluate hypotheses regarding the origin and formation of nonreactive carbon in shelf sediments. Researchers are applying recently developed techniques for the analysis of biopolymers (pyrolysis-mass spectrometry, two-dimensional nuclear magnetic resonance spectrometry, compound-specific stable isotope analyses, and C-14 dating of very recalcitrant carbon by accelerator mass spectrometry) to organic matter samples collected at the sediment-water interface. (RPIS 10677)

Department of Physical Oceanography

612. A Study of Sediment Motion and Bottom Boundary Layer Dynamics Over the Middle Atlantic Bight Shelf and Upper Slope

J. H. Churchill

(508) 457-2015

\$203,000

This project, to be carried out jointly by investigators at North Carolina State University and Woods Hole Oceanographic Institution, aims to clarify understanding of sediment dynamics over the Middle Atlantic Bight (MAB) shelf and slope. To be scrutinized are processes that affect sediment motion in particular, the action that generates turbulence in the bottom boundary layer and the action of towed fishing gear. The research effort includes an instrument development component aimed at upgrading measurement capabilities near the sea floor, a process study of sediment resuspension by bottom fishing gear, and a number of large scale moored instrument deployments over the MAB shelf and slope. The moored instruments programs are the focus of this effort and give measurements of fluid velocity and suspended solids concentration throughout the water column. Four deployments are to be carried to capture the range of sedimentological and dynamical conditions present over the MAB shelf and slope. The ultimate goal is to put together a coherent picture of the near-bottom response to physical forcing over the MAB and its role in the dissipation of incident energy and movement of solid material. (RPIS 10675)

Environmental Processes and Effects: Subsurface Sciences and Environmental Radon

Intramural DOE Laboratories

Argonne National Laboratory

Argonne, IL 60439

Chemical Technology Division

613. Application of High-Sensitivity Laser Techniques to Actinide Speciation in Groundwater Systems

D.T. Reed

(708) 972-7964

\$150,000

This research investigates factors that affect radionuclide speciation and migration in groundwater systems. The emphasis is on interactions between organics, the inorganic species present in groundwater, and the radionuclides present in the contaminated system. Real and simplified groundwater systems are studied.

Radionuclide speciation and migration are investigated via a combination of spectroscopic and potentiometric methods. The work is based largely on the application of two complementary and highly sensitive laser techniques: laser photoacoustic spectroscopy and laser-induced fluorescence. These have general applicability to a wide variety of problems important to radionuclide migration and have demonstrated applicability to actinide speciation in groundwater-like systems.

The research results in an improved understanding of factors that control radionuclide speciation and their mobilization and immobilization in subsurface media. Improved understanding leads to new site-remediation concepts and improved capabilities to predict the migration of co-contaminants in the subsurface. (RPIS 5389)

Environmental Research Division

614. Mechanisms of Colloidal Transport in Groundwater Environments

J.S. Gaffney

K.A. Orlandini

N.A. Marley

(708) 972-5178

\$130,000

Site-directed subsurface studies on groundwater transport of contaminants, performed at Argonne National Laboratory and other laboratories involved in the DOE/OHER Subsurface Science Program, show that the transport of pollutants over large distances can be correlated with the presence of colloidal materials. The mechanisms of this transport, however, are not understood. The goal of this research program, which is part of the Geochemical Transport Processes/Colloids Subprogram, is to determine the mechanisms of colloidal sorption and transport of hydrophobic and hydrophilic contaminants in groundwater. The formation and physical and chemical transformations of colloidal materials in solution during interactions with mixed wastes in groundwater systems must be characterized to accomplish this task. Colloidal materials are collected at natural and contaminated subsurface sites in analytical amounts, using hollow-fiber ultrafiltration with minimal sample perturbation. Particular attention is paid to natural organic colloids and organically coated inorganic colloidal materials. Chemical characterization of these materials is accomplished by using carbon-13 nuclear magnetic resonance spectroscopy, pyrolysis gas chromatography, and elemental analyses (for trace metals and radionuclides). Colloids are size-fractionated by ultrafiltration after particles greater than 0.45 microns in diameter are removed. Sorption studies evaluate the effects on colloid transport properties of changing the subsurface geochemical environment. Of particular interest are colloidal binding of radionuclides and of toxic metals and interactions with hydrophobic contaminants. These studies, performed along with other site-directed subsurface projects that evaluate colloidal transport questions, determine the importance of colloids in groundwater transport of toxic waste. The information gathered is important for potential application of colloids to clean up contaminated sites. (RPIS 5041)

615. Investigation of Organic/Inorganic Complexation Processes in Subsurface Environments*N.A. Marley**J.S. Gaffney*

(708) 972-4910

\$30,000

Because of the widespread nature of subsurface contamination and the need for fundamental information on its transport and transformation, the DOE/OHER established a new research effort, the Subsurface Science Program. Little is known about the transport mechanisms or the chemical speciation of organic-inorganic complexes in subsurface environments and in associated pore and groundwaters. Developing and implementing satisfactory control and containment strategies requires an understanding of the mechanisms of subsurface mobilization of organics, inorganics, and organometallics. Within the Subsurface Science Program, the Co-Contaminant Chemistry Subprogram addresses this need. As part of the Co-Contaminant Chemistry Subprogram, this particular project studies organic-inorganic complexation for naturally occurring humic acids and a number of chelating agents known to be used in mixed-waste cleanup (e.g., ethylenediaminetetraacetic acid, tributyl phosphate, and citrate), along with known microbiological degradation products (e.g., oxalate, and acetate). Laboratory studies evaluate the competitive formation of aqueous chemical interactions because water interferes minimally. When the chemical interactions are qualitatively identified, quantitative speciation occurs by using a variety of spectroscopic, analytic, and radiochemical methods. (RPIS 5174)

Brookhaven National Laboratory

Upton, NY 11973

Department of Applied Sciences**616. Biodegradation of Selected Organic Compounds and Complexing Agents of Radionuclides and Metals***A.J. Francis*

(516) 282-4534

\$280,000

The goal of this research is to examine the microbial degradation of organic-complexing agents that mobilize radionuclides and toxic metals at contaminated sites. The study is investigating the rate and extent of biodegradation of (1) a multidentate chelating agent, diethylenetriaminepentaacetic acid; (2) microbially produced complexing agents (citrate, polysaccharides); and (3) selected organic compounds commonly used in radionuclide and metal extractions and separations, e.g., tributyl phosphate and tetraphenyl boron. Biodegradation under aerobic and anaerobic conditions in culture media and in subsoils with differing physical and chemical properties is being studied. The degradation of these compounds is tested using pure or mixed cultures of micro-organisms isolated from mixed wastes and leachates from disposal sites and using co-metabolic processes in the presence of the other carbon sources. The degradation products are analyzed to

determine whether primary, secondary, or ultimate degradation of the complexing agents has occurred. Successful organisms are to be tested to determine their ability to degrade complexes of uranium and lead, and the fate of released U and Pb is to be determined. The effect of environmental variables, including Eh, pH, temperature, moisture, nutrients, oxygen, and alternate electron acceptors on the rate and extent of degradation is to be elucidated. (RPIS 5042)

617. Role of Micro-Organisms as Regulators of Uranium Mobility in Natural Radioactive Mineral Deposits*A.J. Francis*

(516) 282-4534

\$30,000

The objective of this study is to elucidate the mechanisms by which aerobic and anaerobic microbes, in particular heterotrophs, regulate the mobilization or stabilization (immobilization) of uranium, thorium, and rare Earth elements in radioactive mineral deposits. Natural radioactive mineral samples from the U.S., and from ongoing multidisciplinary international projects such as Pocos de Caldas natural analogue project in Brazil, the Alligator River's analogue project in Australia, and from the Cigar Lake uranium deposit natural analogue project in Canada are being investigated. In the initial phase of this study, aerobic and anaerobic micro-organisms are being isolated from oxidizing and reducing fronts of natural radioactive minerals obtained from the Pocos de Caldas natural analogue project. The basic mechanisms of aerobic microbial dissolution of radionuclides from mineral deposits in the oxidizing front and immobilization by anaerobic microbes in the reducing front are being elucidated. Such natural microbial processes can be exploited in regulating the mobility of radionuclides and toxic metals in wastes, and in contaminated soils and sediments. In addition, microbial cultures isolated from deep sediment samples at Hanford, Idaho, and Nevada test sites are being tested for their ability to solubilize or stabilize radionuclides and toxic metals. Several of the microbes are being selected and tested for use in the bioremediation of radioactively contaminated soils and sediments, and in the biotreatment of radioactive wastes by selective extraction or immobilization of radionuclides and toxic metals. (RPIS 5552)

Department of Chemistry

618. Fundamental Studies of Radon Release from Soil

G. Harbottle

(516) 282-4387

\$115,000

This project addresses one of four major concerns of the DOE/OHER radon program: the question of radon availability in the soil. If radium were homogeneously distributed in soil grains, there would be little opportunity for radon escape, contrary to observation. Thus, this project's goal is to develop a comprehensive picture of the chemical and physical relationships in the loci of the radon precursors on or within soil grains to better understand the mechanisms of radon escape. The experimental approach emphasizes the quality-controlled, quantitative determination of members of natural radioisotope series (uranium, thorium, radium, radon, etc.) present in soils, through measuring their characteristic gamma radiation. These analyses permit determination of (1) the fraction of radioactive emanation atoms, radon and thoron, that can escape the soil grains; (2) the departures from secular radioactive equilibrium existing in radioisotope series found in whole soils and soil fractions; and (3) the analytical concentrations of the radioisotopes. This research seeks to understand the initial step in the radon delivery process, which begins in the soil and ends in the human lung, by formulating and testing models for radon availability. (RPIS 5024)

Idaho National Engineering Laboratory Idaho Falls, ID 83415

Earth, Environment, and Life Sciences Group

619. Hydrogeologic and Geochemical Controls on Micro-Organisms in Subsurface Formations

C.W. Bishop

(208) 526-6782

\$150,000

Understanding the physical and chemical variables that control the diversity and abundance of micro-organisms in the subsurface is critical to quantifying the important mechanisms of in situ bioremediation. Identifying the controlling parameters—the ultimate objective—requires the ability to predict the occurrence of micro-organisms in the subsurface and to determine the conditions under which their growth can be enhanced for remediation purposes. This research is designed to determine the geochemical, hydrological, and hydraulic properties of subsurface systems that exert the most influence on the occurrence of deep subsurface micro-organisms from samples obtained at semi-arid western DOE sites. The role of environmental factors is quantified through characterization of field samples and validation of hypotheses through laboratory experiments.

Comprehensive characterization of previously obtained subsurface samples suggests that transport properties in saturated and unsaturated zones are important controls on microbial numbers, types, and activity. Laboratory column studies using site-specific cores and groundwaters are being

performed to determine the extent to which micro-organisms are transported through subsurface material with different hydraulic properties. Groundwaters are being characterized to identify the nutrients available in the low molecular weight fraction of dissolved organic carbon. The effects of wetting and drying cycles in unsaturated zones are to be quantified through examination of field samples and a set of laboratory microcosm studies. An integrated model of the relative effects of transport and nutrient flux is expected to result from these studies.

Knowledge of the importance of individual hydrologic and geochemical parameters that control the distribution of subsurface microorganisms will lead to the ability to tailor in situ bioremediation processes to specific groundwater systems and aid in the design of cost-effective remedial technologies. (RPIS 5390)

620. Complete Degradation of Mixed Halocarbons by Methanogenic and Methanotrophic Microbial Communities

F.S. Colwell

G.F. Andrews

(208) 526-0097

\$20,000

The goal of this research is to determine the chemical and biological requirements of a mixed methanogenic and methanotrophic community to optimize sequential biodegradation of mixtures of toxic organic solvents in transitional redox zones. The data obtained are being used to (1) mathematically model and predict transport and consumption of contaminants, electron acceptors, and nutrients in an aquifer and (2) predict bacterial growth and production of methane. Laboratory experiments use continuous differential bioreactors to characterize separate methanogenic and methanotrophic communities, to determine (1) their nutrient requirements for microbial degradation of the halocarbons trichloroethylene (TCE) and tetrachloroethylene (PCE) and (2) the concentration levels of TCE and PCE that would inhibit the growth and activity of the microbial consortia. Data from these experiments are used with a mathematical model to formulate the design of a continuous-flow, anaerobic/aerobic saturated sand column. Sand columns with a flow component approximate natural aquifer conditions better than the static experiments can. Subsequent measurements of TCE and PCE degradation, oxygen consumption, production of methane, and the biomass obtained from mesocosm experiments determine the validity of modeled predictions. Information that can be used for in situ and bioreactor treatment of mixed chlorinated hydrocarbons in groundwater is being developed. (RPIS 5175)

- 621. Deep Subsurface Sample Analysis at Idaho National Engineering Laboratory**
R.S. Colwell
G.J. Stormberg
 (208) 526-0097 \$110,000

The goals of this research are to (1) acquire uncompromised samples of deep subsurface materials for microbiological, chemical, and physical analyses and (2) assess the effects of selected aspects of drilling and sampling methodology on the microbial communities in subsurface samples. The primary focus of this project is to analyze high quality samples of deep subsurface materials at the Idaho National Engineering Laboratory (INEL) for microbiological, chemical, and physical analyses. Rock material and groundwater are being sampled at specified depths in a 700-foot test hole at INEL, at a site where the water table is about 460 feet deep. The hole is drilled by the air-rotary method, and several zones are cored and sampled for analyses. Procedures for drilling and sampling involve an air filtration system, the use of an inert gas as a drilling medium above the target zones, decontamination of all equipment, and downhole tracers. The choice of these procedures is based on previous drilling experience at INEL and the Savannah River Site as well as on recommendations developed by the Transitional Deep Microbiology Subprogram Drilling/Sampling Technologies Steering Committee. Within 48 hours of being removed from the hole, all subsurface samples are checked for the presence of tracers, packaged, and shipped to other investigators involved in the transitional phase of the program. Additional experiments are being conducted onsite to determine (1) the possible effects of exposing the subsurface microflora to light and (2) the effects of sample handling and shipping on the numbers and community structure of subsurface microbes. (RPIS 5365)

Radiological & Environmental Sciences Laboratory

- 622. Idaho National Engineering Laboratory Radioecology and Ecology Program**
O.D. Markham
 (208) 526-2164 \$40,000

Studies continue on the rate of invasion and distribution of cheatgrass at the Idaho National Engineering Laboratory (INEL). In the Intermountain West, the invasion of exotic plant species, (e.g., cheatgrass) has been identified as the number 1 non-EPA environmental issue. INEL continues to evaluate spatial and temporal dynamics of cheatgrass. Data management systems are compared to determine which can best predict variations in the dynamics of cheatgrass associated with global climate change.

Publication of data and results continues on a variety of projects; most receive only partial and limited OHER funding. Cooperative studies comparing ecosystem structure and function among other semi-arid DOE sites receive attention. This includes publications on plant productivity and the responses of plant communities to regional changes in the availability of water and nitrogen that could result from future climate changes. (RPIS 1390)

Lawrence Berkeley Laboratory Berkeley, CA 94720

Applied Science Division

- 623. Experimental and Theoretical Investigations of Radon Availability, Migration, and Entry**
R.G. Sextro
H.A. Wollenberg
T.N. Narasimhan
W.J. Fisk
 (415) 486-6591 \$420,000

The purpose of this research is to investigate experimentally and theoretically radon availability, radon transport through soils, and entry of radon into basements as a function of geologic conditions, climate, and basement characteristics. Radon availability refers to the potential of the soil to be a source of high indoor radon concentrations and is thought to be primarily a function of soil radium concentration, soil moisture, and soil permeability. Radon transport within soil occurs by pressure-driven flow of soil gas (which contains radon) and, usually to a lesser extent, by molecular diffusion of radon. Radon entry into basements depends on radon availability, the factors that affect transport (such as soil permeability), basement characteristics (such as size and location of openings to the soil), and the magnitude of the pressure difference between basement and soil. This research seeks to advance and verify theories that will aid in the understanding of radon availability, transport, and entry. The details of the interactions among environmental conditions, soil characteristics, building features, and indoor radon concentrations are poorly understood and existing models are unverified. This project is helping to elucidate these relationships so that indoor radon concentrations and the associated risks can be understood more fully and so that corrective measures and policies can be evaluated. (RPIS 5023)

Earth Sciences Division

- 624. An Interdisciplinary Approach to Spatial Characterization of Contaminant Transport**
E.L. Majer
J.C.S. Long
S.M. Benson
 (510) 486-6709 \$270,000

Characterization of the in situ properties controlling fluid flow is vital to the prediction of contaminant migration in natural systems. This research involves a joint geophysical-hydrologic approach to characterizing and identifying the fundamental properties necessary to map contaminant transport in media at shallow toxic waste sites. The goal of the project is to use geophysical methods to develop an overall understanding of how heterogeneities affect fluid flow in porous media. The approach uses controlled small scale field sites and laboratory information to characterize the properties affecting contaminant flow, which

can be imaged with seismic methods. The result will be an understanding of scale effects and how scaling up affects the physical properties controlling contaminant transport. Initial efforts are being made in defining the hierarchy of physical characteristics that control fluid flow and seismic properties by means of in situ application of high resolution seismic imaging in dispersive and fast path environments. Data collection from dispersive environments has been completed and emphasis is now on fast path media and mixed media. Data from controlled intermediate scale lab experiments are being used to determine the dominant physical characteristics of these environments. The ultimate goal of this project is to determine the optimum seismic and hydrological information necessary to successfully predict contaminant transfer in hydrophysical systems. (RPIS 5256)

625. Experimental Investigation of Thermodynamic Properties of Chemical Species Present in Mixed Organic-Radionuclide Wastes

H. Nitsche

(510) 486-6509

\$140,000

Laboratory research is being performed with the objective of providing fundamental knowledge about the basic chemical processes that occur between radionuclides and synthetic organic chemicals present in mixed organic-radionuclide wastes at DOE sites. This knowledge allows researchers to make more accurate predictions of the processes that control contaminant mobilization and transport in the subsurface environment.

The project experimentally determines the thermodynamic and kinetic solution phenomena (such as complexation constants, speciation, and solubility of complexes) and the nature of compounds that can form between the actinide elements neptunium, plutonium, and americium and selected hydrophilic and hydrophobic organic constituents of mixed organic-radionuclide wastes. The data are necessary for researchers to predict and model the interaction and stability of co-contaminants and their maximum release concentrations in the subsurface. Existing databases used as input for transport modeling are either incomplete or lack data for complexation, speciation, and solubility of most hydrophilic mixed organic-actinide waste complexes and compounds. Results from this experimental program can be used to help fill in these gaps. The results of this task can be used to support the Co-Contaminant Chemistry Subprogram of DOE's Subsurface Science Program. Analysis of the project's results will provide possible pathways for manipulating the geochemistry to achieve remediation by either stabilizing or mobilizing contaminants in the subsurface.

A major part of the effort for this program is focused on collaborative research with other participants of the co-contaminant chemistry subprogram. The collaborations will provide an increased understanding of intermediate- and macro-scale transport of plutonium, cobalt, and chromium with the complexing agents NTA, EDTA, citric acid, and oxalic acid with and without the presence of microbes and surfaces that can adsorb metal ions. The collaborative research team will

produce knowledge of the very complex behavior of organic-radionuclide mixtures in the subsurface much faster and far more comprehensively than any single-investigator effort. (RPIS 5176)

626. The Chemistry of Toxic Organic/Metal Ion (Radionuclide) Co-Contaminants Involved in Subsurface Transport

D.L. Perry

(510) 486-4819

\$125,000

Recent studies have shown that one of the most important mechanisms that affects toxic metal subsurface transport is that of organic complexation. Cobalt, uranium, and chromium all documented health hazards in the biosphere have been shown to undergo a significant increase in ground transport kinetics when complexed with organic molecules as mixed co-contaminants. The experimental database for organic/metal ion co-contaminant systems, however, is relatively nonexistent; virtually no experimental spectroscopic data have been gathered to characterize these organic/metal ion mixtures.

The present research consists of several parts from unique, state-of-the-science instrumental techniques. The first portion involves the synthesis of organic/metal ion complexes involving cobalt, uranium, and chromium with the multidentate chelating carboxylic acids diethylenetriaminepentaacetic acid (DTPA), ethylenediaminetetraacetic acid (EDTA), and cyclohexanediaminetetraacetic acid (CDTA). The second portion of the research involves the use of Auger, x-ray photoelectron, Fourier transform infrared, and Raman spectroscopies to (1) study the chemistry and spectroscopy of the mixed contaminants and (2) devise new analytical approaches for the detection of the mixed contaminants in soil and groundwater.

The data derived from this research will provide an extremely critical experimental chemical base to model hydrologic transport of co-contaminant organic/metal ion species in subsoils and groundwater. (RPIS 5413)

627. An Investigation of Chemical Flow Characteristics Using Fiber Optic Sensor Technology

T.J. Kulp

S.M. Angel

(510) 423-0375

\$140,000

This project is a combined experimental and theoretical effort to gain improved understanding of chemical transport in soils and other porous media by investigating the relationship between transport at the microscopic spatial scale and transport at the macroscopic scale. Many bulk phenomena associated with transport in porous media result from the flow behavior of the system at the microscopic spatial scale. Dispersion, for example, is the result of a number of microscopic phenomena, including the mixing caused by solid obstructions in the flow path, the incomplete connectivity of the medium, eddies, and the recirculation caused by regional pressure gradients. Theoretical modelers of chemical transport in porous systems

derive bulk transport behavior through mathematical volume averages over representative elementary volumes of the matrix. In doing so, assumptions must be made regarding the form of the microscopic variables. Unfortunately, very little is *empirically* known about microscale transport because of the difficulty of measuring flow within the interstices of the solid porous matrix. The project goal is to provide the empirical data.

The immediate target of this investigation is the direct measurement of the interstitial dispersive flux of a chemical species as it is transported through a porous medium and the subsequent comparison of these measurements to the bulk-dispersion coefficient. To accomplish this, it is necessary to measure simultaneously the spatial concentration distribution of the species and the fluid-flow velocity field at high spatial resolution within a solid matrix. This is being accomplished using two high resolution imaging techniques—particle image velocimetry and particle streak velocimetry—to measure velocity and fluorescence imaging to measure chemical concentration. Imaging within the pore spaces of the medium is accomplished by constructing the porous system used in the study of solid and liquid waste materials that have identical refractive indices. The resulting uniformity of refractive index eliminates refraction scattering from solid-liquid interfaces within the medium and allows clear imaging to any point within it. At the present time, these measurements are producing unique data at spatial resolutions that have not been possible in the past. This information will be extremely valuable in assessing the effect of volume-averaging on predictive dispersive flow calculations.

This work is being done in support of the OHER Site-Directed Subsurface Environmental Initiative. (RPIS 4910)

Lawrence Livermore National Laboratory Livermore, CA 94550

Earth Sciences Division

628. Application of Particle Methods to Multicomponent Geochemical Reactive Transport Problems

A.F.B. Tompson

R.B. Knapp

(510) 422-6348

\$140,000

This project applies the particle tracking method to solve equations that describe transport of multiple, reacting chemical components in porous flow systems. In large, multidimensional applications, particle tracking methods can be more efficient than conventional finite difference or finite element models. They can readily account for advection, dispersion, and reaction processes and easily treat sharp reaction fronts with a simple computational algorithm. The particle tracking method uses a large yet finite number of particles to represent the spatial distribution of dissolved chemical mass. A two-stage stepping algorithm is being used to stimulate its movement, dilution, and creation or loss. In each time-step, particles are first displayed according to various flow or diffusive mechanisms. Their masses (or number) are then modified to reflect the influence of chemical reactions or other

gain or loss phenomena. The researchers are examining both kinetic and equilibrium reaction processes that may describe such mechanisms as precipitation, dissolution, ion/isotope exchange, and absorption. Various geochemical modules are being developed and tested within a particle code. Initial applications consider the mathematical verification of the code for simpler problems for which analytical solutions or laboratory experimental data exist. Other simulations involve successively more complicated chemistries, flow systems, or geometries. Additional efforts are devoted to improving the computational efficiency and performance of the relevant algorithms and codes by adapting them for use on parallel and vector architecture computers. Ultimately, applications are oriented toward improving the understanding of specific complex migration and transformation issues at field sites. (RPIS 5177)

Los Alamos National Laboratory Los Alamos, NM 87545

Isotope and Nuclear Chemistry Division

629. Co-Contaminant Reaction Chemistry at Interfaces

P.G. Eller

D.E. Morris

(505) 667-6045

\$180,000

This project consists of an experimental study of fundamental processes underlying the partitioning and chemical alteration of specific organic-radionuclide co-contaminants having direct environmental relevance at nuclear reprocessing and waste storage/disposal facilities. The radionuclides of interest are actinides (e.g., U, Np, Pu) and fission products (e.g., Cs, Sr, Tc, Ru, and I); the principal organic co-contaminants are neutral donor extractants [alkyl phosphates such as tributylphosphate (TBP) and ketones such as methyl isobutyl ketone (MIBK)] and process hydrocarbons (e.g., kerosene, CCl₄). The predominant environmental matrices are common clays (e.g., smectites and kaolinites). The influence of feed solution composition on uptake, release, and chemical alteration of the radionuclide, organic, and solid substrate components is being studied by scintillometry, gamma spectroscopy, x-ray diffraction, and mass spectrometry. Emphasis is being given to determining the speciation of the surface and interlayer co-contaminant complexes using advanced spectroscopic probes including x-ray absorption and photothermal spectroscopies. Initial work on small scale static and dynamic contact experiments evolves to large scale column experiments with applicability to field conditions. The ultimate goal of this project is to develop data useful for developing remediation strategies and establishing predictive capabilities for mixed radionuclide-organic co-contaminant problems at DOE sites involved with plutonium-uranium extraction process and related actinide processing activities. (RPIS 5178)

Oak Ridge National Laboratory

Oak Ridge, TN 37831

Environmental Sciences Division**630. Radionuclides in the Environment***B.G. Blaylock**F.O. Hoffman**M.L. Frank**(615) 576-7397***\$40,000**

Research in this project is directed toward (1) supporting international activities in radioecology involving DOE programs, (2) using radionuclides as quantitative tracers of ecological processes, and (3) investigating the environmental behavior and fate of selected radionuclides in terrestrial and aquatic environments. Current DOE international commitments require DOE participation in a cooperative research agreement with the Commission of the European Communities on the validation of radioecological food chain models, participation in the International Biospheric Model Validation Study, work with the International Atomic Energy Agency, and involvement in a U.S./U.S.S.R. Cooperative Study. Research is continuing on the use of radiotracers to determine (1) the retention of soluble and insoluble constituents in rainfall by plants and (2) the cycling of different chemical forms of selenium in aquatic ecosystems. Studies on the fate of radionuclides in the environment are directed toward determining the role of aquatic macrophytes in the remobilization of radionuclides (Cs-137, Co-60, and Sr-90) from sediments. (RPIS 0690)

631. Soil-Water-Contaminant Interactions*G.K. Jacobs**P.M. Jardine**(615) 576-0567***\$140,000**

The goal of this research is to quantify thermodynamic and kinetic processes that control the mobility of contaminants and co-contaminants in subsurface environments representative of DOE sites. This work is part of the Co-Contaminant Chemistry Subprogram of the Subsurface Science Program. Subprogram goals addressed in this project include: (1) to improve the ability to model multicomponent sorption reactions on DOE site materials, incorporating both inorganic and organic surface interactions; (2) to identify inorganic and organic solid phases in subsurface materials with which contaminants associate over long inground contact times; (3) to identify key organic-inorganic co-contaminant interactions in the aqueous phase and on surfaces to develop models and descriptive data to describe and predict their effects; and (4) to identify dominant long-term attenuation/contaminant geochemical processes in the field. The objectives of the research are (1) to elucidate adsorption processes for contaminants and co-contaminants on representative fracture-filling minerals (e.g., calcite) for incorporation into hydrogeochemical transport models relevant for application at DOE sites and (2) to determine thermodynamic and

kinetic parameters for solute transport models used to assess in situ contaminant mobility in heterogeneous soils. Results will provide a link between microscopic scale mechanistic studies of sorption and field-scale studies. Initially, Sr, Co, and ethylenediaminetetraacetic acid (EDTA) have been emphasized. Successful implementation of the research methods suggests that additional contaminants (e.g., actinides; ^{99}Tc , Cs, Hg, and other organic acids; chelating agents; and natural colloids) and soils representative of several other DOE sites be investigated. Past accomplishments include (1) partial completion of Ca-Sr-Co-EDTA ion exchange and transport studies in one heterogeneous soil type; (2) partial completion of studies of Sr, and initiation of Co, adsorption onto natural calcite; and (3) presentation and publication of results. (RPIS 5179)

632. Subsurface Transport Model Validation and Uncertainty Analysis in Heterogeneous Field Soils*P.M. Jardine**V. Wilson**(615) 574-8058***\$140,000**

The basic goal of this research is to quantify transport processes at varying spatial scales. These data are used to develop a transport model for chemically reactive and nonreactive contaminant solutes that incorporates multiple pore-size processes and that can be validated by the field-scale experimental results. Experiments are conducted at the Melton Branch Watershed experimental facility in eastern Tennessee, where the hydraulic and chemical properties of the soils have been well characterized. At the field location, one-dimensional (vertical) unsaturated transport experiments are made on an in situ soil pedon. During storms, both conservative (bromine) and reactive (potassium, magnesium, and dissolved organic carbon) tracers are released from a buried line source for two-dimensional transport studies and from a 0.67-hectare catchment for three-dimensional transport studies. Samples collected from field lysimeters in the vadose zone and from subsurface weirs are analyzed to determine the extent of inorganic and organic contaminant transport in the subsurface environment. Process information determined from these data is used to assess, modify, and validate the FEMWATER and FEMWASTE transport codes and to allow the incorporation of transport information at multiple pore scales. Stochastic simulations are used to determine uncertainties caused by complex natural spatial heterogeneities. These simulations are also used to determine the minimum data needed to predict contaminant transport in heterogeneous media. (RPIS 5180)

633. Field-Scale Validation of Multispecies Transport*P.M. Jardine**(615) 574-8058***\$20,000**

This research addresses the issues of DOE's Subsurface Science Program and the goals of the Field-Scale Experimentation and Multi-Component Predictive Models Subprogram. The purpose of this research is to develop, verify, and validate a generic three-dimensional fluid flow and multispecies hydrogeochemical transport model to assess field-scale multispecies contaminant transport problems. The specific objectives of this project are to: (1) spatially characterize the key subsurface chemical and physical properties controlling contaminant mobility on a field facility at Oak Ridge National Laboratory (i.e., Melton Branch Watershed), (2) apply geostatistical methods to conditionally simulate realization of input parameters at all three-dimensional gridpoints from spatially distributed field measurements in (1), (3) develop a three-dimensional fluid flow and hydrogeochemical transport model equipped with an efficient and accurate numerical algorithm, and (4) validate the generic three-dimensional model in (3) with measured fluxes and chemical distributions from the field facility using input parameters obtained in (1) and (2). Spatial characterization of the field-site physical properties have been nearly completed in previously funded DOE initiatives (Subsurface Transport Model Validation - Jardine/Wilson/Yeh). The current research stresses the spatial characterization of chemical properties at the field facility and these include (1) soil indigenous cations and anions, (2) soil pH, (3) soil cation and anion exchange capabilities, (4) competitive electrostatic interactions, and (5) soil surface complexation reactions. Because it is not possible to make field measurements at all possible three-dimensional gridpoints for application, geostatistical techniques are used to simulate hydrologic and geochemical parameters at all three-dimensional grid points using the measured data above. The spatially characterized experimental data are then used as input parameters for a newly developed three-dimensional fluid flow and multispecies hydrogeochemical transport model. Successful field-scale modeling requires an efficient and accurate numerical algorithm which is accomplished by modifying the Lagrangian-Eulerian approach with a new adaptive local grid refinement that greatly reduces the number of nodes to be zoomed yet improves the accuracy of the computations. The predictive capabilities of the model are compared to storm-driven multispecies solute transport studies conducted at the field facility in 1990-1991. Potential validation of the model allows engineers to develop remediation strategies for complex waste sites targeted at specific problems and with a higher probability of success. (RPIS 5624)

634. Colloidal Mobility Experiments Using Natural Organics*J.F. McCarthy**P.M. Jardine**L. Liang**(615) 576-6606***\$475,000**

The transport of colloidal particles in groundwater is being studied to improve capabilities to predict the subsurface transport of contaminants that sorb to mobile colloids. The project objectives are to (1) determine if colloids are mobile in subsurface environments and (2) elucidate the chemical, hydrological, and mineralogical properties of aquifers that influence colloid transport. Mobility of colloidal organic matter (COM) was observed following a forced gradient injection of a COM solution into a sandy coastal aquifer in South Carolina. The breakthrough curves of COM at sampling wells displayed many features predicted from laboratory soil column studies, including (1) rapid breakthrough of a slowly sorbing component, (2) absence of size exclusion, (3) slow tailing to long times, (4) very slow desorption of COM, and (5) fractionation of COM into fast and slower moving components. However, the retardation of COM observed at the field site was much less than the retardation predicted from laboratory studies, possibly due to either a physical process (preferential flow), or a chemical one (competition between solid and solution phase iron for COM). Oxygen present in the injection solution resulted in oxidation and precipitation of iron (hydroxide) particles in some sampling wells; however, in most wells, an oxygen plume was not observed even after several weeks of injection. Oxygen may have been consumed by oxidation of Fe(II) or of COM. One- and two-dimensional hydrological modeling of the experiment are in progress. Continuing field experiments and supporting laboratory studies on the interaction of COM and iron (both solid and solution phases) and redox controls of those interactions improve understanding of the chemical and hydrophysical processes controlling COM mobility and the formation, stability, and transport of iron colloids. This research also tests strategies for manipulating colloids to improve environmental restoration. These goals are relevant to DOE needs for understanding pathways of contaminant transport. (RPIS 5172)

635. Characterization and Microbial Utilization of Organic Carbon*J.F. McCarthy**A.V. Palumbo**P.M. Jardine**(615) 576-6606***\$175,000**

The goals of this research are to (1) characterize the particulate and dissolved (or colloidal) organic matter occurring in deep subsurface environments, and (2) assess the potential of these sources of organic matter to serve as a nutrient source for microorganisms in deep subsurface environments. This research will characterize natural organic matter in water and aquifer material from different geologic formations sampled in the

Deep Microbiology Subprogram and will examine the ability of subsurface bacteria to use these sources of organic matter for growth. The discovery of diverse groups of bacteria at depth in subsurface environments raises questions about what nutrient sources exist for the microbes and what part microbes may play in degrading contaminants in groundwater. The role of natural organic matter is central to both issues. Organic matter may be a source of nutrients that can reach great depth. Furthermore, sorption of persistent organic contaminants to the organic matter may change the availability of the contaminants for microbial degradation; elucidation of this effect is a long-term goal of the project. To improve understanding of the organic matter in groundwater, the chemical and structural properties of organic matter in water and on aquifer surfaces from deep subsurface formations will be characterized to elucidate properties relevant to (1) the subsurface transport and mobility of the organic matter and (2) the potential role of organic matter in groundwater and sorbed to particles as a nutrient source supporting microbial productivity in the deep subsurface environment. The bioavailability of organic matter as a nutrient source for subsurface microbiota will be assessed by measuring the ability of organic matter, or fractions of the organic matter, to stimulate bacterial growth (measured as cell count, thymidine and acetate incorporation). The bacteria used will be isolates from the Deep Microbiology Subprogram or microbial assemblages. (RPIS 5433)

636. Mobility of Micro-organisms in a Sandy Aquifer

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R.C. Bales

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R.S. Burlage

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\$60,000

Field-scale research, with supporting laboratory experiments, examines the geochemical, hydrological, and biological factors controlling the mobility and survival of microorganisms at the field scale. Well-defined bacteria and other tracers will be injected into a well-characterized and well-instrumented aquifer and recovered at several downgradient sampling wells. The goal of the field experiments is to identify and understand newly emergent properties expressed only at the field scale and develop new models that include consideration of the scale of physical and chemical heterogeneities that affect microbial transport. A second goal is to determine the survival of non-native (introduced) microorganisms under the specific conditions at the research sites. The objectives of the field experiments are to (1) quantify biocolloid transport over a range of spatial scales, (2) test the importance of microbial properties that influence bacterial mobility at the laboratory scale (e.g., size and surface properties) on transport at field scale, (3) evaluate scales of physical and chemical heterogeneity that affect biocolloid transport in natural aquifers, and (4) determine the long-term survival of introduced bacteria.

Development and validation of specific and sensitive molecular probes is a key aspect of this research so that several different biocolloids strains with a range of properties postulated to influence transport can be injected simultaneously into the aquifer and the transport of each strain enumerated using strain-specific molecular probes. (RPIS 5556)

637. Mixed-Waste Biodegradation

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\$20,000

The goal of this research is to maximize the rate and extent of biodegradation of mixed organics in co-contaminated waste without increasing the mobility of radionuclides. The specific target, ethylene diaminetetraacetic acid (EDTA) complexed to Co-60, is found at a number of DOE sites including Oak Ridge National Laboratory (ORNL) and is very difficult to degrade. The objective is to degrade EDTA to reduce the mobility of Co-60 at the site. Growth substrates and conditions for EDTA degradation by bacteria, obtained by isolation or in collaboration with other investigators, are being determined. Subsurface materials are being recovered from a representative DOE waste storage area at ORNL and used in laboratory columns and batch experiments to determine degradation rates and contaminant fates during mixed-waste biodegradation. Tests are initially being conducted using ¹⁴C labeled EDTA along with co-metabolites identified (e.g., glucose), electron acceptors (e.g., oxygen), and nutrients (e.g., phosphate, ammonia, and trace minerals). Varied mixtures of organic contaminants found at the site (e.g., xylene, toluene, naphthalene, and trichloroethylene) are being added. Effects of these different treatments on degradation rates and the mobility of the Co-60 are being measured. The results of this study should provide the basis for determining if bioremediation of a mixed-waste site contaminated with EDTA is feasible or even desirable. (RPIS 5183)

638. Subsurface Microbial Ecology of GEMHEX and Triassic Basin Samples

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\$60,000

The project goal is to determine geological and biological factors that support long-term microbial survival in subsurface environments. This research is developing a conceptual understanding of bacterial activities, growth, and survival in the terrestrial subsurface. Conceptual models are consistent with field observations, providing credence to the hypothesis of bacterial survival. Knowledge gained through this proposal complements Subsurface Science Program (SSP) program goals and objectives by examining bacterial survival, transport phenomena, and adaptation in deep subsurface environments.

Field sampling opportunities have focused on Pacific Northwest Laboratory's GEMHEX sampling and the

exploratory origins borehole with Texaco in the Taylorsville Triassic Basin. Tasks have included enumeration and enrichment of microbial trophic groups, estimation of metabolic potentials, isolation of micro-organisms, and experiments examining nutrient limitations. Differences among surface, subsurface, and geologically isolated microbial communities were noted from the Triassic Basin site, with aerobic communities predominating in near-surface sediments and transitioning to thermophilic anaerobic saline-tolerant anaerobes at depths exceeding 8,000 ft. below land surface. In addition to enumeration and potential metabolic capability studies, GEMHEX analyses have focused on nutrient limitations. Preliminary results support the hypothesis that subsurface microbial survival is limited by nutrient availability, particularly the availability of phosphorous. Laboratory experiments utilizing the recently obtained isolates are investigating (1) geochemical factors facilitating survival, (2) physiological characteristics, and (3) unique traits of micro-organisms in the deep subsurface. Future experiments will examine the effects of altered environmental conditions on the growth and survival of novel saline-tolerant thermophilic anaerobes. This research is expanding knowledge of microbial abundance, diversity, capabilities, and traits in diverse environments. (RPIS 5741)

Health and Safety Research Division

639. Investigation of Radon Entry and Effectiveness of Mitigation Measures

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\$100,000

The objective of this research program is to gain better understanding of radon transport and factors affecting mitigation efficiency. The focus of this research is the investigation of availability and transport near occupied houses. A noteworthy aspect of this research is the effort to understand and model the impact on radon transport of near-surface, natural fissures, or other inhomogeneities. In addition, the researchers seek to evaluate the nature of radon transport at two sites in the southern Appalachian region. These sites exhibit very different patterns of correlation between radon in the house and radon in nearby fissures. Population-based risk assessments currently rely on exposure data gathered from screening surveys of indoor radon levels. The estimation of clustering (i.e., geographic distribution) of indoor radon levels is an integral part of extrapolating survey results to the larger population. To date, a small fraction of single-family detached dwellings has been monitored for radon. An even smaller fraction of rooms in large structures (e.g., schools, office buildings, and factories) has been monitored. With the current work by several research groups on radon transport in homogeneous media, this work on the effects of large (1 to 20 cm) pores and crevices on radon transport into houses should increase understanding of house-to-house varia-

tion within neighborhoods. This will reduce the uncertainty in population exposure estimates that will be extrapolated from current or future survey results. (RPIS 4850)

Pacific Northwest Laboratory Richland, WA 99352

Environmental Science Department

640. Subsurface Microbial Phenomena

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\$225,000

Previous investigations by this project have demonstrated that indigenous microbial populations have an important role in governing the persistence and transport of organic contaminants within subsurface environments. However, biodegradation of organic compounds in mixtures is not scientifically well understood. Fundamental investigations are being performed to examine (1) the microbial, metabolic, and genetic processes governing the behavior of organic compounds within subsurface environments and (2) the chemical and hydrological properties that control microbial metabolic activity and metabolism. This research directly addresses the Biodegradation/Microbial Physiology Subprogram goals: (1) to improve the understanding of the aerobic and anaerobic microbial transformation of organic compounds in contaminant mixtures, (2) to develop a research base for the molecular genetics of organic catabolism in subsurface bacteria, and (3) to develop a mechanistic understanding of the interactions between biodegradation and sorption of organic compounds. The biodegradation of organic contaminants, selected on the basis of their relevance to DOE sites and groundwater contamination nationwide, is investigated by looking at the contaminants both individually and in the presence of co-contaminants where co-contamination occurs at DOE sites. Information on the biochemical pathways utilized and their genetic control is being developed. The induction of aromatic degradative genes in subsurface bacteria, the effects of cell starvation on induction, and rates of bio-degradation are being determined. The primary sources of organisms are subsurface sediments and groundwater sampled from the DOE sites. Experiments are being performed to provide a generalized understanding of the biodegradation of organic contaminants that undergo sorption reactions. (RPIS 4285)

641. Deep Subsurface Microbiological Investigations

J.K. Fredrickson

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\$570,000

Previous investigations have demonstrated the presence of diverse bacteria in Southeast Coastal Plain subsurface sediments ranging from 50-1,500 ft. Microbial populations have been shown to be very diverse even at a scale of less than 1 m. However, a general understanding of the geochemical and physical properties of deep subsurface environments that

control microbial presence, distribution, and activity is lacking. Microbiological investigations at DOE sites that differ from the DOE Deep Microbiology reference site (Savannah River) are being conducted to identify the diversity, activities, and metabolic potential of the subsurface microbiota. The metabolic potential of subsurface microbiota in saturated and unsaturated subsurface environments is being probed using an enrichment matrix approach that consists of groupings of electron donors (monomers, polymers, fermentation products, and aromatics) and electron acceptors O_2 , NO_3^- , $Fe(III) + Mn(IV)$, SO_4^{2-} , and CO_2 . Vadose zone sediments are being obtained to investigate the phenomena of resuscitation of microbial activity, a phenomenon first identified by this project. The project attempts to determine the physical, chemical, and biological factors promoting the observed, time-dependent increases in microbial activity following sample collection. This knowledge is being then used to develop strategies for in situ stimulation of microbiota in unsaturated sediments, as a novel variation of in situ bioremediation. These strategies are being evaluated in column and field studies. This research addresses the following Deep Microbiology Subprogram short- and long-term goals: (1) to characterize and compare microbial communities and their environments in geochemically and hydrologically diverse subsurface systems; (2) to identify and investigate subsurface microbial physiological and genetic traits relevant to biodegradation or stabilization of contaminants; (3) to quantify vertical and spatial variability of composition and function of subsurface microbial communities on several scales; (4) to develop improved drilling, sampling, and sample-handling methodologies for obtaining microbiologically and chemically uncompromised subsurface samples; (5) to develop the ability to predict subsurface microbial metabolic capabilities from geochemical and hydrologic data; and (6) to conduct experiments under controlled conditions to compare usefulness of using native or introduced microbial populations. (RPIS 5229)

642. Subsurface Chemistry of Organic Chemical and Organic/Radionuclide Mixtures

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\$800,000

The purpose of this research is to investigate interfacial geochemical reactions of subsurface materials to chemical mixtures in order to improve reaction-based models of sorption and abiotic degradation used to predict contaminant concentrations in subsurface environments. The scientific focus is on multispecies interactions between organic substances and inorganic contaminants (e.g., metals, radionuclides) such as competitive sorption, cosorption, and cosolvation. Organic substances (humic materials, organic acid complexing agents, and organic solvents) and metals/radionuclides (U, Co, Pb, Cs, Sr, and Tc) representative of chemical constituents on DOE lands are used in carefully selected mixtures to test surface chemical hypotheses about multispecies interactions. Laboratory experimentation involves the contact of these mixtures with (1) subsurface materials having diverse mineral

and chemical properties, (2) natural clays, oxides, and organic matter isolated from subsurface sediments, and (3) reference mineral/organic surfaces. Various instrumental techniques employed to investigate the nature of the multispecies surface reactions include laser microelectrophoresis, luminescence spectroscopy, and calorimetry. Multispecies, multisite surface complexation models are employed to evaluate hypotheses regarding dominant surface reaction mechanisms, reactive contributions of different sorbents, and the effects of different co-contaminant interactions. Collaborative studies with another Pacific Northwest Laboratory project are investigating the influence of the same interfacial geochemical processes looked at in this research on microbiologic transformations of organic and inorganic species. The long-term goals of collaboration are development of (1) a generalized reaction-based geochemical model incorporating complex organic-inorganic contaminant interactions, and (2) new concepts for subsurface chemical remediation. (RPIS 5173)

Environmental Sciences Research Center

643. Radon Transport Modeling in Soils

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\$130,000

This project constructs, validates, and applies a comprehensive computer-based model (Rn3D) of radon transport within soils and from soils into structures and the atmospheric environment. Rn3D simulates three-dimensional transient transport of radon in variably saturated, heterogeneous porous media. The principal outputs of the model are time-varying radon fluxes at the soil surface or basement floor/wall and subsurface concentrations of radon gas.

The model will solve all pertinent differential equations governing the transport of radon, soil gas, liquid and vapor water, and energy. All the equations, boundary conditions, and soil properties will be computer based to examine unsteady-state heterogeneous soil problems around three-dimensional structures over considerable time periods. Model validation will be comparison of field data with computer model comparisons.

Studies of model input parameter sensitivity and uncertainty are being completed for both homogeneous and heterogeneous soils. Applications of Rn3D could include supporting the development of measurement criteria for soils, interpretation of aeroradiometric studies, interpretation of meteorological effects, linking with building transport and human exposure models, and analyzing radon mitigation measures. (RPIS 5026)

644. Chemical Remediation Concepts: Bioremediation Concepts*R.E. Wildung**F.J. Brockman*

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\$1,900,000 (5142A - D)

This research is part of Pacific Northwest Laboratory's Environmental Sciences Research Center's coordinated experimental and theoretical investigations in molecular biology, which are being performed to (1) introduce and express important biodegradative enzymes and to redesign them to extend the substrate range of subsurface bacteria for DOE site contaminants and (2) test the biodegradative capacity of these bacteria in culture and in intermediate scale flow cells which simulate the subsurface environment. Bacterial strains from the deep microbiology transition phase sediments are being used. Initial work focuses on the introduction and expression of the enzyme toluene dioxygenase, which cometabolizes trichlorethylene (TCE), in subsurface bacteria. Because expression currently requires a toxic inducer (e.g., toluene), genes are being placed under the control either of a constitutive promoter or of a regulatable promoter from a different operon where the inducer can be used in the environment. The ability of bacterial strains to maintain introduced genes and degrade the target contaminant under conditions which simulate the subsurface environment (i.e., hydrodynamic flow in porous media and competition with indigenous microflora) is being tested. The *Pseudomonas putida* P-450cam enzyme is being redesigned to produce enzymes able to degrade contaminants that concern DOE. The initial focus is on chlorinated hydrocarbons (e.g., trichloroethylene), but this focus will be extended to include synthetic chelate (e.g., ethylene diaminetetraacetic acid)-radionuclide complexes. Amino acid substitutions shown by molecular modeling and molecular dynamics simulations to allow catalytic attack of the target contaminant are being introduced into the P-450cam gene. The redesigned enzymes are being assayed in vitro and introduced into subsurface bacteria, and the bacteria are being tested for degradative ability in culture and in flow cells. (RPIS 5142(A))

645. Manipulation of Natural Subsurface Processes: Field Research and Validation*R.E. Wildung**J.S. Fruchter**J. Zachara*

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The investigators are examining and testing hypotheses in the field regarding the ability to manipulate aquifer geochemistry. Such manipulations have the ultimate objective of assisting natural processes to restore contaminated subsurface sites at DOE facilities. The scientific hypotheses are derived in part from fundamental research and pertain to the manipulation of in situ geochemical and microbiologic processes to alter aquifer geochemical parameters such as pH, redox potential, and sorptivity in a controlled manner. Field experimentation entails injection and withdrawal to create a small forced gradient

system that has the advantages of well-defined initial conditions, the ability to control the movement of solutes, and minimal volume to be characterized. Reagents designed to temporarily alter the geochemical status of the aquifer are being injected, and their effects on both the aqueous and solid phases are being assessed through water and core sampling. The system's response is being used to quantify the nature and magnitude of fundamental processes and their interaction in controlling the behavior of select chemical species in the subsurface. The first phase of the effort entails experimentation at laboratory and intermediate scale and modeling to help define a detailed experimental plan to be evaluated in a national workshop. The field experiment then develops fundamental knowledge of the nature and kinetics of both water/rock and microbially mediated redox reactions in the actual subsurface. Other hypotheses center on the response of the integrated system to chelating compounds and the complex subsurface mechanisms governing microbial viability and function. This project addresses the Subsurface Science Program goals to establish a national field manipulation site and to test promising concepts for manipulating natural phenomena. (RPIS 5142(B))

646. Chemical Desorption, Dissolution, and Partitioning*R.E. Wildung**C.C. Ainsworth*

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Reactions that control the release of sorbed contaminants from subsurface materials (e.g., desorption and dissolution) are being examined to identify geochemical strategies to enhance contaminant mobilization and to hasten restoration of waste sites. Research emphasizes desorption/dissolution of contaminants (Cs, Sr, Cu, U, Co, PAHS, PCBS, and others) that associate with the solid matrix and, with time, become increasingly difficult to displace to the aqueous phase. Contaminants revert to less extractable forms as the result of at least four mechanisms that incorporate contaminants into or within many geologic and soil materials: (1) recrystallization, (2) lattice penetration, (3) crystal overgrowth, and (4) micropore diffusion. Experiments are being carried out, using (1) subsurface materials from contaminated and uncontaminated DOE sites, (2) natural mineral phases isolated from subsurface materials, and (3) reference mineral phases of known properties that control contaminant mobility. Both contaminated materials from DOE disposal sites and contaminant-spiked materials are being used to determine how long contaminant residence times (up to 40 years) affect the distribution, leachability, and release rates of contaminants. A combination of batch- and flow-type kinetic techniques is being used to determine (1) the rate-controlling reactions involved in contaminant desorption/dissolution; (2) the influence of such variables as pH, ionic strength, and aqueous composition; (3) the presence of co-contaminants modifying single contaminant reactions; (4) the residence time on these rate-controlling reactions; and (5) the ability of chemical additives (e.g., complexants or surfactants) or geochemical manipulation to influence the rate of mobilization and the partitioning of contaminants. (RPIS 5142(C))

647. Microbial Sequestration and Bioaccumulation of Radionuclides and Metals

R.E. Wildung

H. Bolton, Jr.

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Radionuclide and metal contaminants are present in relatively inaccessible zones in the unsaturated and saturated environments at DOE and many other sites. These contaminants can migrate and enter domestic groundwater supplies. Economic approaches to remediate or stabilize these deep contaminated zones are limited. One promising process for inorganic contaminant immobilization is the sequestration or bioaccumulation of mobile radionuclides and metals by subsurface micro-organisms. Sequestration is the complexing of inorganic ions with ligands, which can result in either mobile or immobile complexes; bioaccumulation is a specific microbial process of sequestering aqueous ions with cell biomass associated ligands. Most subsurface micro-organisms are attached to the solid phase so that bioaccumulation of mobile radionuclides and metals would reduce their transport. This project will determine (1) the capacity, selectivity, and mechanisms of bioaccumulation of subsurface micro-organisms and (2) how geochemical and growth conditions influence the bioaccumulation process. Subsurface micro-organisms are being used in batch and column studies to determine the kinetics of inorganic contaminant bioaccumulation during growth and the subsequent release rates during starvation. The nutritional and geochemical conditions are being altered to obtain a generalized understanding of these processes in subsurface environments. Finally, sediment samples from a radionuclide and metal contaminated site will be manipulated in the laboratory, using information and organisms obtained from this project to reduce inorganic contaminant transport under simulated subsurface conditions. This project will therefore provide an enhanced understanding of the sequestration and bioaccumulation of radionuclides and metals that will help develop more accurate predictive models of inorganic waste migration and effective strategies to remediate radionuclide and metal contaminated sites. metals, inorganic contaminants, subsurface, transport. (RPIS 5142(D))

Geosciences Department

648. Chemistry/Microbiology Controlling Chelated Radionuclide Transport

H. Bolton, Jr.

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\$270,000

Increased radionuclide transport in the subsurface environment can occur when radionuclides are codisposed with synthetic chelating agents. This enhanced transport due to mixed-waste disposal is caused by the formation of chelate-radionuclide complexes that adsorb to subsurface sediments less than unchelated radionuclides. Chelated radionuclides are therefore more mobile. The objectives of this project are to

(1) determine the surface chemical and microbiological properties of chelated radionuclides and (2) determine the interactions that control their stability, persistence, retardation, and mobility in subsurface environments with various chemical, microbiological, and lithological properties. Batch experiments are being used to investigate the sorption/desorption behavior of Co and Am and the chelating agents ethylene diaminetetraacetic acid, diethylenetriaminepentaacetic acid, and NTA on several important sorbents (e.g., metal oxides of Al and clay separates from subsoils along with DOE-site subsoils) under varying geochemical conditions (e.g., pH, electrolyte concentrations, presence of competing native cations). Similarly, batch experiments are using subsurface sediments and micro-organisms to determine the rates of degradation for chelating agents and the geochemical/microbiological factors controlling these rates (e.g., pH, Eh, alternative C source, complexed metal). Integrated studies of chemistry and microbiology are being performed in batch and column modes at the intermediate scale to investigate chelate adsorption-biodegradation interactions and the influence of redox potential on chelated radionuclide fate. This project is providing currently unavailable information and a conceptual understanding of the (1) subsurface microbiological degradation of chelates, (2) adsorption/desorption of chelated radionuclides, (3) speciation of the chelates and radionuclides during these processes, and (4) influence of environmental conditions on these processes. This information is needed to assess and mitigate the problem of chelate-mediated radionuclide transport at DOE sites. This research will allow DOE researchers to predict the persistence and movement of chelated radionuclides based on site-specific knowledge of microbial populations, groundwater geochemistry, and saturation zone lithology and hydrologic properties. It will also develop effective site remediation strategies and technologies. (RPIS 5044)

649. Deep Microbiology Geosciences Testing

P.E. Long

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\$500,000

Understanding the physical and chemical variables that control the diversity and abundance of micro-organisms in the subsurface is critical to eventual use of micro-organisms for in situ remediation of hazardous waste sites. The ultimate goal of such understanding is the ability to (1) predict the occurrence of micro-organisms in the subsurface and (2) determine conditions under which their growth can be enhanced for remediation purposes. A suite of hydrogeologic and geochemical parameters is needed on samples collected adjacent to those samples previously analyzed for micro-organism type and abundance, to evaluate the parameters significant to microbiological populations in the subsurface environment. Identification of significant factors helps DOE establish the potential use of subsurface microbes for (1) destroying organic wastes by metabolic processes, (2) altering subsurface hydraulic properties, or (3) manipulating

ing radionuclide transport characteristics. This project contributes directly to meeting the following scientific goals of the Deep Microbiology Subprogram of the Subsurface Sciences Program: (1) to characterize and compare microbial communities and their environments in geochemically and hydrologically diverse subsurface systems; (2) to identify the chemical and physical environmental factors that most strongly influence subsurface microbial communities and their metabolic activities; (3) to develop the ability to predict subsurface microbial presence, diversity, and activity from geochemical and hydrologic data; and (4) to quantify vertical and spatial variability in the composition and function of subsurface microbial community on several scales. (RPIS 5391)

650. Pore Water Chemistry

J.P. McKinley

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\$100,000

This project provides analytical and sampling support to field activities within the Deep Microbiology Program and conducts research on the relationship between microbial populations and their aqueous chemical environment. Support of field activities includes (1) analysis and evaluation of aqueous chemical tracers, (2) determination of pore water and groundwater compositions, and (3) analysis of regional geochemical trends and their relationship to dominant microbial processes affecting or affected by groundwater compositions. Pore water compositions in core samples are being determined either by direct pore-water expression or by a method of multiple-leaching steps followed by extrapolation for each ion of interest. Field-related experiments are evaluating the accuracy, precision, and practicability of this approach. The benefit of these experiments will be a previously nonexistent estimate of chemical variation in pore water on a fine scale. Original laboratory research is being used to evaluate the effect on microbial metabolic rates of amendments to pore water composition in the unsaturated zone. Fixed amounts of organic nutrients are being injected into unsaturated sediments along with varying concentrations of inorganic nutrients and other ions. The rate of utilization of the organic nutrients is being compared to the input aqueous composition. The benefit of this research is a direct evaluation of the effects of variations in nutrient chemistry on in situ bacteria at a DOE site. This project supports Deep Microbiology Program requirements for (1) coquantification of chemical and microbial distributions, (2) determination of pore water and groundwater compositions, (3) effect of composition on microbial diversity and capabilities, and (4) investigation of chemical contaminants on microbial populations. (RPIS 5127)

651. Microbial Origin/Transport in Subsurface Systems

E.M. Murphy

B.D. Wood

P. Long

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\$300,000

The goals of this research are (1) to determine if microbial communities were transported to where they are now found in deep subsurface systems or if they are relics of the original depositional environment, and (2) to investigate how changes in the geochemistry may have influenced microbial evolution and respiration. The origin and transport of micro-organisms in groundwater are poorly understood but are probably controlled to a large degree by the geochemical environment and the availability of carbon substrates and electron acceptors. The origin of micro-organisms in subsurface sediments may be by (1) evolution in situ from organisms entrained in the original sediments, (2) transport through the aquifer from the recharge zone, or (3) a combination of these two sources. Measurements of groundwater age and of unsaturated and saturated transport rates will give the most accurate information on the minimum amount of time that the micro-organisms have evolved in situ. The maximum amount of time that the micro-organisms have been entrained in the sediments can best be addressed by a combination of sediment dating and paleogeography. In specific aquifer systems, the chemical evolution that occurs along a horizontal flow path will be analogous to the changes that occurred in the water chemistry during vertical deposition of the sediments. In situ microbial communities deposited with the original sediments will have evolved in response to changes in this geochemical environment. In turn, the presence of micro-organisms affects both the chemical and isotopic composition of groundwater and its geochemical evolution along groundwater flow paths. Reaction-path modeling of the geochemistry along groundwater flow paths provides detailed information on subsurface biogeochemical processes, leading to a better understanding of the distribution, diversity, and activity of micro-organisms in groundwater. The fractionation of stable isotopes (isotopes of carbon, sulfur, nitrogen, and possibly iron) can be incorporated in reaction-path models to simulate microbial geochemical reactions. By simulating these microbial reactions, the in situ activity or respiration rates of micro-organisms in the subsurface can be estimated. Stable isotope signatures allow us to identify relevant sources and sinks and to directly attribute portions of product to biotic and abiotic processes. (RPIS 5626)

652. Subsurface Organic Fluid Flow

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\$365,000

Organic components in energy-related waste at DOE sites present a hazard to the subsurface environment. The hazard occurs because these components are commonly immiscible, nonaqueous-phase liquids that can migrate separately from prevailing groundwater flows. To protect public health, enhanced predictive computer models are needed to assess the

potential for subsurface migration of organic liquid contaminants. Before such models can be accurately devised, advances are needed in the fundamental understanding of multiphase, immiscible flow processes in subsurface media. Proven techniques for obtaining the constitutive parameters for such models are also required. Pacific Northwest Laboratory is performing a series of basic experiments both in laboratory columns and intermediate scale flow cells to examine mechanisms of immiscible flow in aquifers and vadose zones. The flow experiments measure organic liquid retention and conduction behavior under nearly natural, yet controlled, intermediate-scale conditions. This work is part of the research plan of the Multiphase Fluid Flow Subprogram of the OHER Subsurface Science Program, as described in DOE/ER-0432. This research contributes to the following program goals: (1) transferring the subprogram experience in multiphase fluid movement to assist in the demonstration of cleanup of hazardous organic liquids at one DOE site (FY 1992), (2) completing a series of intermediate scale experiments to identify effects of heterogeneity on immiscible organic liquid flow in porous media using a subsurface experimental research facility (FY 1993), and (3) developing improved predictive modeling ability to assist in remediation actions and site restorations involving harmful organic liquids found in the subsurface of DOE sites (FY 1995). (RPIS 5143)

653. Intermediate Scale Subsurface Transport of Co-Contaminants

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\$450,000

Multidimensional solute transport experiments in layered porous media are being performed using multicontaminant solutions subject to chemical sorption and abiotic-microbiologic transformation. Ancillary column experiments are also being performed. These studies are needed to improve predictions of contaminant behavior in subsurface environments contaminated by complex mixtures that exhibit spatial heterogeneity in porous media. This work addresses research goals of the Coupled Processes Subprogram by conducting intermediate scale experiments to quantify (1) the interaction of sorption and biodegradation during transport and (2) the unique phenomena that may occur at media interfaces. Specific objectives of this research include determining (1) the effect on reactive transport of porous media layering, (2) variation in sorption mechanisms within a suite of contaminants, and (3) microbial population heterogeneity. Studies begin in well-characterized media with representative compounds and progress to natural materials with DOE site-specific contaminant mixtures (e.g., organic solutes/solvents, organics/radionuclides). This work explicitly accounts for interaction between sorption and degradation processes. Multidimensional flow cells containing layered (stratified) media, with horizontal saturated water flow, are instrumented to measure water movement as well as contaminant and electron acceptor concentrations at in situ locations. Mathematical/

numerical transport models are used to premodel experiments for optimizing design parameters and for analysis/simulation of experimental data. The experiments are being done in the Subsurface Environmental Research Facility (SERF) at Pacific Northwest Laboratory. This project is also managing SERF and collaborating with other DOE projects helping them design intermediate scale experiments to be conducted at SERF. (RPIS 5045)

Environmental Processes and Effects: Subsurface Sciences and Environmental Radon

Offsite Grants

University of Arizona

Tucson, AZ 85721

Department of Hydrology and Water Resources

654. Transport of Subsurface Biocolloids in Porous Media

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\$106,000

Investigations focus on the adhesion and transport properties of subsurface bacteria in porous media. The goal is to develop and validate quantitative tools to predict and interpret biocolloid movement in the field under varying chemical conditions.

Subsurface bacteria are cultured and screened for stickiness using filtration, electrophoretic-mobility, phase-partitioning, and contact-angle methods. The hypothesis is that deep bacteria grown on low-nutrient media have electrophoretic mobility, hydrophobicity, and stickiness (α) like that of their surface counterparts. The main differences are expected to be in size, shape, and motility rather than in surface-chemical properties. Organisms that have commonly been isolated from the subsurface and deep subsurface are studied. Continuous-flow laboratory column studies (breakthrough type) are used to study the attachment and detachment of biocolloids under simulated field conditions, with varying media and solution-chemical conditions. It is thought that stickiness (α) is sensitive to small changes in the mass-fraction organic carbon of the porous media. Motility should result in enhanced diffusive transport and thus inoculation of porous media. The motility of bacteria exhibiting low stickiness is tested using an experimental apparatus suitable for sampling low concentrations of bacteria passing through samples of consolidated and unconsolidated media.

Larger-scale transport experiments are carried out in intermediate-scale flow cells constructed by Pacific Northwest Laboratory, and/or an intermediate-scale facility being constructed at the University of Arizona. The transport database to be developed is used for modeling the chemical interactions involved in one-dimensional transport. The model incorporates physical, chemical, electrostatic, and growth components. The research is a necessary step toward developing biocolloid-transport models based on fundamental physical and chemical principles and applying those models to intermediate-scale and field situations.

The movement of biological colloids is important because (1) subsurface migration of biocolloids is an important determinant of subsurface ecology, (2) introduction of mobile bacteria or enzymes into contaminated aquifers is a potential in situ cleanup strategy, and (3) colloidal material contributes to aquifer clogging. The ability of bacteria native to subsurface and deep-subsurface environments to migrate may be especially important to their survival, making these organisms attractive candidates for a study of biocolloid transport. (RPIS 10501)

655. Stochastic Analysis of Macrodispersion in Unsaturated Heterogeneous Porous Media

T.-C.J. Yeh

(602) 621-5943

\$115,000

The objectives of the study are to (1) investigate factors controlling the fate and transport of contaminants in heterogeneous unsaturated soils, (2) develop a computationally feasible methodology for predicting chemical movements in field-scale unsaturated zones, and (3) assess uncertainties in predictions due to spatial variability of hydrologic and geochemical parameter values in the field.

To accomplish these objectives, a three-dimensional numerical model for the simulation of water flow and fate and transport of contaminants in the variably saturated zone was developed. The model uses a highly efficient finite element approach and modified method of characteristics to resolve many difficult problems in simulating flow and transport in highly heterogeneous porous media.

For assessing uncertainties in prediction of chemical transport in unsaturated zones, a new iterative condition approach, using conductivity and matric potential measurements, has been developed. This new approach permits the examination of the interactions of spatially varied hydrological, geochemical, and biochemical factors controlling the fate and transport of contaminants, bacteria, and colloids in the subsurface environment. In addition, it allows the design of sampling schemes for reducing the uncertainties in the predictions.

To achieve the interdisciplinary goal of the Subsurface Science Program, the numerical model developed in this project has been employed to assist the design of field experiments and interpretation of the results of the experiments, conducted by researcher of colloids and biocolloid

subprogram for the study of mobility of natural organic matter in aquifers. (RPIS 10500)

University of California, Irvine
Irvine, CA 92717

Department of Civil Engineering

656. Surface Chemistry Investigation of Colloid Transport in Packed Beds

T.M. Olson

(714) 856-7188

\$105,000

The goal of this research is to determine which physico-chemical parameters in the interactions between colloidal suspensions and collector surfaces are important to describing particle deposition from first principles. Researchers are assessing and validating predictions of how surface chemistry interactions affect colloidal filtration and suspension in aquifer media and how these interactions govern fine particle mobilities in groundwater. Spectrophotometric measurements are being taken, using crystalline (-quartz) and amorphous silica glass beads packed in columns and suspensions of negatively charged inorganic colloidal particles in the submicron-to-micron-size range; variations in particle concentrations on the different surfaces are being determined. Scanning electron microscopy is being used to determine the colloid deposition patterns and assess the role of aggregation in colloid deposition and mobility. (RPIS 10038)

Colorado State University
Fort Collins, CO 80523

Department of Radiology and Radiation Biology

657. Effects of Vegetation on Radon Transport Processes in Soil

T.B. Borak

(303) 491-5343

\$134,000

Research has shown that vegetation can alter soil properties by removing moisture through evapotranspiration and dynamic root patterns. This could change the conductivity or provide alternate routes for radon migration. This information is also required for the development of computerized radon transport models. This research determines how radon concentrations in subterranean structures are influenced by atmospheric conditions (temperature, barometric pressure, wind, precipitation) and soil conditions (moisture, permeability, porosity), including the indoor-outdoor gradients of pressure, temperature, and radon concentrations; tests the hypothesis that deep-rooted plants might increase the flow of radon into the atmosphere, thus measurably reducing the transport into subsurface spaces; and provides the data for experimental testing of radon transport models.

A research facility has been designed and built to carry out the objectives of this study. Two virtually identical subterranean structures have been constructed, one to serve as the test (e.g., including vegetation) and the other to serve as a control (e.g.,

without vegetation). The concept is unique because the structures resemble miniature basements using conventional construction techniques, but eliminate other confounding factors introduced by occupant activities. (RPIS 9662)

Cornell University

Ithaca, NY 14853

Department of Microbiology

658. Comparison of Distribution, Abundance, and Activities of Deep Subsurface Micro-Organisms at DOE Sites

W.C. Ghiorse

E.L. Masden

(607) 255-3086

\$30,000

The goals of this research are (1) to examine deep subsurface materials for the presence and abundance of micro-organisms (with direct microscopic methods), (2) to characterize a broad spectrum of microaerophilic organisms that may be present in these materials, and (3) to correlate subsurface hydrologic and geochemical data with microbiological activity. Samples of geochemically and hydrologically diverse subsurface materials are obtained from the Savannah River Site, the Idaho National Engineering Laboratory, and the Hanford Site. The total number of micro-organisms in these samples is determined with direct microscopic methods, such as the acridine orange direct count procedure. Cultural methods (e.g., most-probable-number analyses and plate counts on a variety of nutrient media) are used to determine the number of viable micro-organisms and to study subsurface microbial metabolic activities. A special effort is being made to enumerate, isolate, and characterize obligate and facultative microaerophilic organisms (including methanotrophs) in the samples. The resulting data, along with those from other microbiologists involved in the Subsurface Science Program, will then be correlated with chemical, physical, and hydrologic data on the samples (obtained by other investigators). The correlated data will (1) provide a comprehensive description of microbial diversity and community structure in each sample and (2) identify the specific hydrologic and geochemical environmental parameters that most significantly affect the composition and activities of the subsurface microflora. (RPIS 10315)

University of Delaware

Lewes, DE 19958

College of Marine Studies

659. The Effect of Bacteria and Microbial Metabolites on Mineral Dissolution in Subsurface Environments

W.J. Ullmann

D.L. Churchman

P. Vandevivere

S.A. Welch

(302) 645-4302

\$108,000

The goal of this research is to determine if and, if so, how aerobic bacteria can affect the solubility and dissolution rates of minerals commonly found in aquifer rocks. Specifically, the research focuses on the effect of microbially produced extracellular polymers and organic acids on the rate of dissolution of members of the plagioclase feldspar series, quartz and calcite, all common aquifer minerals. The hypothesis is that insoluble polymers may decrease dissolution rates of minerals by coating reactive surfaces. Low molecular weight organic acids should increase the dissolution rate by complexing structural metals at the mineral surface. Ultimately, this knowledge may be useful in developing bioremediation strategies for regulating aquifer permeability by varying the inorganic nutrients and carbon sources provided to subsurface bacteria.

Studies survey bacterial strains from the Subsurface Microbial Culture Collection and other sources to identify those that affect mineral dissolution rates. Batch cultures of minerals and bacteria or minerals and additional known or model bacterial metabolic products are performed. Different combinations of nutrient concentrations and ratios, bacterial strains, and mineral compositions are tested using this approach. Glucose is the primary carbon substrate. When strains with dissolution enhancing or inhibiting behavior are identified, more-controlled experiments are performed using flow-through reaction vessels, analogous to traditional chemostats, where the composition of input solutions and flow rate can be regulated over time. The flow-through strategy permits almost continuous observations of bacterial metabolic status, mineral solution rate, and the behavior of a single culture. Subsequent experiments examine the role of alternate carbon sources (acetate, natural polymers such as chitin, cellulose, proteins, and hydrocarbon analogue of petroleum) on bacterial metabolic products and therefore mineral dissolution rates. (RPIS 10492)

Parachem Technology, Inc.

Springfield, OH 45505

660. Field-Portable Instrumentation for Metal Analysis

E.J. Taylor

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\$49,862

Field-portable instrumentation suitable for onsite metal analysis is needed. Such instrumentation should permit (1) analysis in real time, (2) simultaneous detection of various metals, and (3) detection levels down to parts per billion. In Phase I, the suitability of an electrochemical measurement concept to achieve these performance characteristics is established. Phase I consists of the following tasks: (1) use of platinum microelectrodes to study detection of selected metals; (2) fabrication of microsensor band electrode arrays; and (3) evaluation of the microsensor band electrode arrays. Furthermore, it demonstrates that the electrode configuration used in this instrument is economical to manufacture.

The commercial applications of metal analysis instrumentation with ppb detection limit and rapid turnaround include (1) characterization, monitoring, and remediation of hazardous waste sites; (2) industrial effluent monitoring; and (3) water monitoring. (SBIR)

Florida State University

Tallahassee, FL 32306

Department of Biological Sciences

661. Phylogenetic Diversity Analysis of Deep Subsurface Micro-Organisms

D.L. Balkwill

R.H. Reeves

(904) 644-5719

\$310,000

This project studies the phylogenetic traits and diversity of deep surface micro-organisms with restriction fragment-length polymorphism (RFLP) analysis and 16S ribosomal ribonucleic acid (rRNA) sequencing. An analysis of the physiological traits of bacteria isolated from deep subsurface sediments at the Savannah River Site in the first phase of the Deep Microbiology Subprogram indicated that most of the sediments contained a surprisingly large diversity of aerobic, chemoheterotrophic bacteria (15 to 65 physiologically distinct strains per sample). Because these bacterial isolates were not identified, however, it was not possible to quantify the actual extent of the diversity present (i.e., it was not possible to determine whether each sample contained several similar strains or a wide range of genera, families, etc.). Similarly, research showed that different geological formations at the site contained physiologically distinct groups of bacteria, but it was not possible to quantify the differences among formations. Some of these unanswered questions are addressed by phylogenetic analysis of bacteria isolated from the Savannah River Site sediments. Because of the large number of strains involved, the isolates are first screened by RFLP analysis. This analysis groups the isolates

into clusters of identical or closely related strains. Selected representatives from each of these clusters (as well as all strains that do not cluster with other strains) are then analyzed with 16S rRNA sequencing, making it possible to place the isolates within established broad taxonomic groups and to determine how distantly related are the different clusters and independent strains (those that do not cluster). Analysis of the resulting data makes it possible to better quantify the diversity in each sediment and to better define the differences in microbial community structure in different geological formations. After the Savannah River Site isolates are analyzed, the work will be extended to micro-organisms isolated from other DOE sites during the transitional phase of the Deep Microbiology Subprogram to permit site-to-site comparisons and correlation with chemical, physical, and hydrologic data obtained by other investigators. (RPIS 10320)

662. Establishment and Maintenance of a Subsurface Microbial Culture Collection

D.L. Balkwill

(904) 644-5719

\$135,000

This project establishes and maintains the Subsurface Microbial Culture Collection (SMCC), a centralized DOE depository for microbial strains isolated from subsurface environments. SMCC initially houses microbial strains isolated from deep subsurface sediments at the Savannah River Site in Aiken, South Carolina, during the first phase of the Deep Microbiology Subprogram. As new cultures are obtained during subsequent phases of the program, SMCC will house subsurface microbial strains isolated from the Idaho National Engineering Laboratory, the Nevada Test Site, the Hanford Site, and elsewhere. SMCC serves as a centralized facility from which established cultures can be obtained and in which new cultures can be deposited. SMCC also maintains a centralized database that can be accessed by investigators with approved research proposals and that provides detailed information on all microbial strains in the collection. The routine activities and services of SMCC include (1) safe preservation of microbial isolates to avoid genetic changes that might limit their usefulness in future investigations; (2) distribution of preserved cultures on request; (3) partial characterization of deposited strains (including determination of cultural, morphological, and physiological traits); (4) continual updating of the SMCC database; and (5) preparation of documents describing the collection and its services. (RPIS 10336)

Golder Associates, Inc./Idaho National Engineering Laboratory
 Richland, WA 99352/Idaho Falls, ID 83415

Earth, Environmental, and Life Sciences Group

663. Drilling and Sampling Technology Research

B.F. Russell

F.S. Colwell

(509) 943-1019/(208) 526-0097 \$182,000/\$251,000

The goals of this research are to (1) coordinate the development of innovative drilling and sampling strategies to collect microbially and chemically representative samples from the subsurface environment, (2) provide onsite hydrogeological expertise to field operations at the Idaho National Engineering Laboratory and the Hanford Site, (3) develop and refine hard-rock sampling techniques, and (4) assess strategies for selecting bioremediation field sites. Aseptic sampling strategies and methods for field sampling operations using air-rotary techniques are critical to obtaining representative sub-surface samples for microbiological and hydrogeological/geochemical research. As part of this research, alternative tracers that ensure aseptic conditions during air-drilling operations are being developed. In consultation with drilling and sampling experts nationally, the investigators review and assess the adequacy of field protocols by field testing. Recommended modifications to drilling and sampling strategies are incorporated into field procedures. Techniques for obtaining microbiological samples from subsurface sediments and rock formations are evaluated, using laboratory experiments. Existing drilling technology is enhanced by determining the effects of temperature on samples and adjusting drilling procedures accordingly. Investigators are helping select a bioremediation site and other field sites. (RPIS 10765/RPIS 5134)

University of Hawaii at Manoa
 Honolulu, HI 96822

Institute of Geophysics

664. Radon Transport in the Subsurface Environment: Natural Response and Structure-Induced Effects

D.M. Thomas

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\$60,000

This research characterizes and quantifies the mechanisms by which meteorological and soil physics variables affect radon transport processes in the subsurface environment, defines the modes of interaction between dwelling floors/walls with soil vapor transport processes at the building/soil interface, and develops a numerical model that adequately describes the radon transport processes in natural and construction-disturbed soils.

Two field sites are being monitored: one at which test and control arrays of radon and soil physics monitoring instruments are buried at three depths in the soil, and a second at which soil

gas radon activities adjacent to an occupied dwelling and in undisturbed soil at a distance away from the dwelling are being monitored. At the first site, the test array has been exposed to a variety of imposed variations in soil conditions—moisture, vertical permeability, hydraulic conductivity—and the response at the test array has been compared with natural radon activities at the control array. At the second site, the radon response is being compared to natural environmental variables both in disturbed soil adjacent to the basement walls and in the undisturbed soil around the dwelling. As a baseline is established for the second site, monitoring of radon activities inside the dwelling will be initiated to determine mass balances of radon transport out of the soil to the atmosphere and horizontal transport through the basement walls.

Numerical modeling of the radon response aims to develop a model that can accurately describe the radon response to both the natural and induced variations in soil physical variables and to meteorological variations. (RPIS 9824)

University of Illinois
 Urbana, IL 61801

Department of Civil Engineering

665. Fundamental Quantitative Analysis of Microbial Activity in Aquifer Bioreclamation

B.E. Rittmann

A.J. Valocchi

(217) 333-6964

\$31,000

The goals of this research are to (1) evaluate experimentally the mechanisms that control the formation of biologically active zones (BAZs) in porous media, (2) examine biodegradation kinetics for specific contaminants within the BAZ, and (3) assess the effect of BAZ formation on aquifer permeability. The resulting data are used to evaluate and further develop a mathematical model to predict the effect of BAZ dynamics on groundwater hydrodynamics and contaminant transport. Experiments use flow-through columns and permeameter with glass beads or sand as the porous medium. One group of experiments evaluates biodegradation kinetics for very low solubility hydrocarbons, which form a separate phase. Permeameter studies use populations with varying carbon/nitrogen ratios to assess how variations in pH, pe, exopolysaccharides, and mineral precipitates affect pore clogging. Evaluating the role of these mechanisms in permeability loss is a key factor in controlling clogging. Two-dimensional modeling describes the factors studied experimentally as well as the effects of moderate heterogeneity. (RPIS 9892)

The Johns Hopkins University Baltimore, MD 21218

Department of Geography & Environmental Engineering

666. Release of Oxide-Bound Toxic Metals by Naturally Occurring and Contaminant-Derived Organic Compounds: The Role of Complexant, Reductant, and Adsorptive Characteristics

A.T. Stone

(410) 516-8476

\$78,000

Organic compounds encountered in the subsurface possess a wide range of complexant donor groups that have substantially different capacities for binding hard (Co^{III} , U^{VI}), borderline (Co^{II}), and "soft" (Hg^{I} , Hg^{II} , Pb^{II}) toxic metal contaminants. In order to evaluate whether toxic metal complexation takes place, interaction of organic complexants with other dissolved metal constituents (e.g., Ca^{2+} and Mg^{2+}) and organic complexant adsorption onto hydrous oxide surfaces must also be accounted for. Organic compounds encountered in the subsurface possess a wide range of reductant functional groups, which exhibit dissimilar capacities for reducing higher-valent forms of the toxic metals previously listed. Rates of organic reductant reaction with toxic metal species must be compared with rates of reductant consumption by subsurface oxidants such as O_2 , $\text{MnO}_2(\text{s})$, and $\text{FeOOH}(\text{s})$; indirect changes in toxic metal speciation arising from dissolution of host sorptive phases and the generation of other sorbing species (e.g., Fe^{II} and Mn^{II}) must be accounted for.

In this work, representative low molecular weight organic compounds and NOM-containing subsurface samples are added to hydrous oxide suspensions containing toxic metals such as cobalt, lead, mercury, and uranium. Changes in toxic metal oxidation state, solubility, and speciation are explored in relation to the complexant, reductant, and adsorptive characteristics of the added organic constituents. The goal of this work is to improve the ability to predict toxic metal speciation and the potential for migration at contaminated subsurface sites. (RPIS 10198)

Massachusetts Institute of Technology Cambridge, MA 02139

Department of Civil Engineering

667. Colloids in Groundwater: Their Mobilization, Subsurface Transport, and Sorption Affinity for Toxic Chemicals

P.P. Gschwend

(617) 253-1638

\$138,000

The overall objective of this research is to develop the means to quantify the roles of colloids in groundwater for enhancing the subsurface transport of toxic chemicals. First, conditions that allow the release of existing soil colloids into the flowing

groundwater, especially when dissolution of secondary cementitious phases like iron oxides or calcium carbonates is involved, are being investigated. Colloids in groundwater and aquifer solid samples are examined for evidence of the mechanisms of colloid-aquifer solid attachment. Aquifer solids are also tested in the laboratory for solution conditions that permit colloid detachment. Second, predictive understanding of the sorption of organic compounds to colloids (e.g., kaolinite, organic macromolecules) is being established. Suspensions of colloidal sorbents are incubated with a suite of organic sorbates exhibiting varying hydrophobicities. Understanding (1) colloid mobilization and (2) toxic compound sorption to these colloids should allow researchers to estimate resultant enhancement in subsurface transport. This result is relevant to the risk associated with existing buried waste sites, the choice and design of future waste disposal sites, and the potential for remediation of sites through manipulation of the colloids present. (RPIS 10028)

University of Michigan Ann Arbor, MI 48109

Civil Engineering Department

668. The Influence of Interfacial Properties on Two-Phase Liquid Flow of Organic Contaminants in Groundwater

K.F. Hayes

(313) 763-9661

\$140,000

The objective of this research is to investigate how changes in interfacial properties affect the flow of an immiscible organic phase in porous media. More specifically, the objective is to develop a comprehensive, quantitative theory to relate how modifications of interfacial structure affect capillary pressure-saturation relationships by (1) identifying interfacial properties responsible for wettability changes, (2) establishing quantitative relationships between these interfacial properties and the degree of wettability, (3) assessing how these relationships are affected by changes in groundwater conditions and the introduction of co-contaminants, (4) examining capillary pressure-saturation relationships as a function of wettability, and (5) developing a methodology for predicting the changes in capillary pressure-saturation relationships from a knowledge of the interfacial properties of an aquifer. Interfacial properties will be evaluated by making spectroscopic, adsorption, and interfacial charge measurements. Wettability is determined by using liquid-liquid interfacial tension and contact angle measurements. Data from the interfacial properties and wettability measurements are then correlated with primary drainage and spontaneous imbibition capillary pressure-saturation measurements. This work provides a framework for predicting changes in capillary pressure-saturation curves from a knowledge of interfacial properties. This information can be used not only in the modeling of multiphase flow from

hazardous waste sites but also in the design of aquifer rehabilitation strategies. (RPIS 10030)

Michigan State University
East Lansing, MI 48824

Department of Crop and Soil Science

669. Physicochemical and Microbiological Factors Influencing the Bioavailability of Organic Contaminants in Subsoils

S.A. Boyd

(517) 353-3993

\$131,000

The objective of this project is to evaluate physicochemical and microbiological factors that influence the bioavailability of soil-bound nonionic organic contaminants. The contaminants used in this study are naphthalene and phenanthrene. The physicochemical parameters for study include the water solubility of the solute, the nature and quantity of the sorbent organic phase, and contaminant aging. Each parameter is expected to influence bioavailability by affecting the desorption kinetics of the soil-bound organic contaminants (i.e., the desorption rate constant and the fractional distribution of the contaminant between the labile and nonlabile sorptive phases). Recent results show that the biodegradative bacteria themselves may also strongly influence the bioavailability of sorbed contaminants. The microbiological factors being studied are substrate affinity, microbial attachment, and motility and chemotaxis. These physicochemical and microbiological factors are studied systematically in batch and flow-through systems. (RPIS 10034)

University of Nevada
Las Vegas, NV 89154

Desert Research Institute

670. Spatial Variability of Deep Subsurface Micro-Organisms and Correlation with Hydrogeologic Parameters

R.J. Jacobson

C.E. Russell

R.A. Wharton

P.S. Amy

(702) 798-8882

\$100,000

The goals of this research are to (1) characterize microbial communities in consolidated subsurface materials at the Nevada Test Site, (2) quantify the spatial variability of the subsurface microflora on small and large scales, and (3) investigate the effects of hydrologic and geochemical environmental parameters on subsurface microbial community structures. The presence, abundance, diversity, and spatial distribution of micro-organisms in the deep subsurface environment at Rainier Mesa on the Nevada Test Site are being investigated. Rainier Mesa contains an extensive tunnel complex that allows access to many

sampling points with a minimum of mining and coring. The three-dimensional spatial variability of microbes on small and large scales is being determined by comparing the composition of the subsurface microbial community in different samples. The significance of starvation survival is being assessed, and the ability of selected isolates to withstand dehydration is being determined in cooperation with other investigators. The microbiological data is being correlated with hydrogeologic and geochemical parameters measured from the same samples. Novel culture profiles that entail minimal time and resources are being developed, and the effect of ground-water geochemistry on micro-organisms is being investigated. A single site in one of the mesa tunnels is being examined to obtain initial samples, determine small scale spatial variability, and perfect methodologies. Two additional subsurface sites are being investigated with the focus on the "pathways" through which water and micro-organisms can infiltrate the rock matrix. The local groundwater flow system is being sampled near recharge and discharge points to determine whether variations in the microflora exist. Soil samples and near-surface rocks are also being sampled for similar parameters. (RPIS 10245)

New Mexico Institute of Mining and Technology
Socorro, NM 87801

Biology Department

671. Water Potential in Relation to Numbers and Activities of Microbes in Saturated and Unsaturated Subsurface Environments

T.L. Kieft

(505) 835-5321

\$69,000

The goal of this research is to investigate the influence of decreased water potentials (both solute and matric) on the abundance and activities of micro-organisms in deep subsurface environments. Low solute water potentials occur in saline aquifers; low matric water potentials occur in unsaturated zones. Samples of subsurface materials from the Savannah River Site, the Idaho National Engineering Laboratory, the Hanford Site, and the Nevada Test Site are being studied. Several of these sites have extensive unsaturated aquifers. Intact cores from both saturated and unsaturated zones are being obtained. Water potentials and water contents of samples are being measured. Numbers of halo- and desiccation-tolerant microbes are being quantified. The spatial heterogeneity of water potentials, microbial numbers, and microbial activities within sample cores are being measured. Carbon-14-labeled organic substrates are being used to measure the potentials for biodegradation of organic substrates by subsurface microbes under conditions of reduced solute and matric water potential. Rates of microbial activity are being related to solute and matric water potentials. (RPIS 10261)

Department of Geoscience**672. Mathematical and Geological Approaches to Minimizing the Data Requirements for Statistical Analysis of Hydraulic Conductivity Distributions***F.M. Phillips**J.L. Wilson**(505) 835-5540***\$55,000**

The basic goal of this research is to develop a methodology for incorporating qualitative geological information into quantitative models of aquifer heterogeneity. This project is an intensive field investigation of the spatial patterns of permeability in a fluvial deposit. Tens of thousands of permeability measurements are being obtained with a portable air minipermeameter. In conjunction with the empirical study of permeability patterns, a geologic study of the sedimentary features is being performed. This will make it possible to determine the relationship between geologic sedimentary features and patterns of permeability. With this information, statistical methods by which the qualitative geologic information can be incorporated into quantitative geostatistical descriptions of spatial variability of permeability in fluvial aquifers will be investigated. Three studies of permeability distributions have already been completed. Because both hydraulic conductivity and permeability are linearly related to the air flow rate data collected, statistical analyses can be performed on the air flow rate data. The results thus far indicate that the estimated statistical parameters correspond to the geologic features observed in the field. Additional data are being collected to expand this relatively small scale study. (RPIS 10027)

673. A Geological Approach to Characterizing Aquifer Heterogeneity*F.M. Phillips**J.L. Wilson**(505) 835-5540***\$122,000**

Spatial variation of hydraulic conductivity has generally been recognized as the dominant medium-dependent control on the transport and dispersion of contaminants in groundwater. Mathematical models that use statistical descriptions of the hydraulic conductivity spatial distribution are available to predict contaminant transport. Such models are expected to be major tools in dealing with contamination problems at DOE sites. Unfortunately, the statistical parameters needed for such models can presently be obtained only through geostatistical analysis of large numbers of permeability data. Both the costs and risks associated with obtaining a sufficient number of measurements in highly contaminated aquifers are very large. This study addresses three fundamental questions: (1) How do depositional processes dictate real-world permeability correlation structures? (2) How can the parameters of these correlation structures be estimated in the field under realistic constraints of time and expense? (3) What mathematical

models will adequately simulate realistic spatial distributions of permeability? The first question is being addressed by completing a detailed comparison of geological structures and permeability geostatistics, over all scales of interest, on an extensive outcrop of an alluvial aquifer. The second question is explored with the aid of geotomography as a subsurface visualization tool. The tomographic data can be interpreted in geostatistical terms with the aid of threshold-crossing theory and other mathematical approaches. Finally, comparison with our extensive data set is used to evaluate the suitability of various mathematical models for synthesizing realistic permeability fields. (RPIS 10739)

674. Small Scale Laboratory Studies of Flow and Transport Phenomena in Pores and Fractures: Phase II*J.L. Wilson**(505) 835-5308***\$101,000**

Small scale laboratory experiments, equipped with an ability to actually observe behavior on the pore level using microscopy, provide an economical and easily understood scientific tool to help validate concepts and assumptions about the transport of contaminants. These experiments offer the propensity to discover heretofore unrecognized phenomena or behavior. The main technique employs etched glass micromodels, composed of two etched glass plates, sintered together, to form a two-dimensional network of three-dimensional pores. Flow and transport behavior is observed on a pore or pore network level and recorded on film and video tape. This technique is coupled with related column studies. Specific examinations include (1) multiphase flow behavior of relevance to liquid-liquid mass transfer (solubilization of capillary trapped organic liquids); (2) liquid-gas mass transfer (in situ volatilization); (3) mathematical models of multiphase pressure-saturation relationships; (4) colloid movement, attachment, and detachment in the presence of fluid-fluid interfaces; (5) bacteria colonization and motility in porous systems; and heterogeneity effects on multiphase flow, colloid movement, and bacteria behavior. (RPIS 10738)

Department of Physics, Research, and Development**675. Transport of Radon and Thoron at the Earth's Surface***S.D. Schery**(505) 835-5341***\$132,000**

This research objective is to better understand transport of radon isotopes through porous media and their release to indoor and outdoor environments. Areas of emphasis include the disequilibrium of radon isotopes near the Earth's surface, the sources and behavior of thoron in indoor environments, and mechanisms controlling the release of radon from soil.

New data are being obtained outdoors near the Earth's surface for concentrations of radon gas and radon decay products in the attached and unattached states. The measure-

ments are being performed in terrains of different roughness (forest through bare sand) under variable atmospheric conditions. Auxiliary measurements to characterize the advective/diffusive transport near the ground include meteorological parameters such as wind speed and direction, insolation, temperature at several heights between 0.2 and 10 meters, aerosol concentration, and size distribution. Direct estimates of diffusion coefficients are made with tracer experiments using smoke. Collaboration with facilities that have state-of-the-art meteorological instrumentation, such as Mauna Loa Observatory, are being pursued. Computer models are being developed to interpret observations in terms of aerosol concentration, atmospheric turbulence, and pertinent meteorological parameters. Thoron and thoron progeny are being monitored in houses undergoing mitigation for radon using subfloor depressurization techniques. Observation of the effect of these mitigation systems on the indoor thoron and thoron progeny is a powerful tool for determining what fraction of the thoron is coming from the soil. Supplemental data such as ventilation rates, outdoor thoron levels, thoron flux from walls, indoor aerosol concentrations, and indoor pressure patterns are being obtained and should facilitate improved models of the sources and behavior of indoor thoron. (RPIS 9821)

University of Notre Dame

Notre Dame, IN 46556

Department of Civil Engineering and Geological Sciences

676. Hydrodynamic Controls on Particle Transport Through Heterogeneous Porous Media

S.E. Silliman

M. Babic

(219) 239-5380

\$128,068

Particle transport through porous media is important for a number of applications of interest to DOE, including colloid transport, biodegradation, nutrient delivery through encapsulation, and alteration of hydraulic properties. The present project focuses on the hydrodynamic controls that influence the relative motion of particles and chemicals in saturated and/or partially saturated media. The primary hypothesis of this effort is that both the potential for movement of particles and the rate of motion of these particles is dependent on the geometric dimension of the physical heterogeneity present within the porous medium. This hypothesis is being addressed through extensive intermediate-scale experiments on artificial porous media exhibiting physical heterogeneity in two and three dimensions. Products to be derived from this effort include an enhanced understanding of the hydrodynamic mechanisms controlling particle transport in saturated and partially saturated media, an extensive database for particle transport in heterogeneous media, and a comparison of the experimental data with predictions derived from particle transport models. Selection of specific heterogeneities to be studied (and selection of particles to be utilized) in this effort is based, in part, on cooperation with other projects within the

Subsurface Science Program, including work in the Coupled Processes Subprogram on chemical and biological transport, work within the emerging Heterogeneity Subprogram, and work in the Colloids Subprogram. (RPIS 10585)

Oregon Graduate Center

Beaverton, OR 97006

Department of Environmental Science & Engineering

677. Adsorption of Chromate/Organic Acid Waste Mixtures in Aquifer Materials

W. Fish

C.D. Palmer

(503) 690-1099

\$44,000

The goals of this research are to determine the mechanisms that govern (1) the adsorptive properties of organic acids on oxide mineral surfaces, (2) the interaction of organic acids with chromate and other anionic contaminants on mineral surfaces, and (3) the mobility of mixtures of organic acids and inorganic anionic contaminants in natural porous media. The sorption behaviors of chromates, selected anions, and a series of alkyl organic acids are being investigated for single constituents and for mixtures on both synthetic goethite (iron oxide) and natural aquifer material from contaminated DOE sites. A variety of analytical techniques (including x-ray diffraction, Fourier-transform infrared spectroscopy, isotope dilution, high performance ion chromatography, and chemical titrations) is being used to characterize the structure of the oxide surfaces and to quantify the equilibrium solution concentration of sorbed species, as well as the surface-complex speciation. These data interpretations are to be used (1) to identify the molecular scale binding mechanisms of organic acids and chromate; (2) to quantify the macroscopic binding parameters of chromate, organic acids, and co-existing anions (such as sulfate) both on the well-defined iron oxide mineral surface of goethite and on the components of natural aquifer materials; (3) to characterize to what extent and under what conditions organic acids compete with chromate for surface binding and to understand the mechanisms of noncompetitive binding; and (4) to improve equilibrium models of adsorption of complex mixtures of anionic pollutants. In later years, transport experiments will be performed with chromate-organic acid mixtures in an intermediate scale experimental aquifer to test the applicability of multispecies equilibrium parameters for predicting co-contaminant transport. (RPIS 10037)

Pennsylvania State University

University Park, PA 16802

Department of Civil Engineering

678. Field-Scale Validation and Development of a Three-Dimensional Fluid Flow and Multispecies-Hydrogeochemical Transport Model

G.T. Yeh

(814) 863-2931

\$42,736

This research the issues of DOE's Subsurface Science Program and specifically the goals of the Field-Scale Experimentation and Multi-Component Predictive Models Subprogram. The purpose of this research is to develop, verify, and validate a generic three-dimensional fluid flow and multispecies hydrogeochemical transport model to assess field-scale multispecies contaminant transport problems. The specific objectives of this project are to: (1) spatially characterize the key subsurface chemical and physical properties controlling contaminant mobility on a field facility at Oak Ridge National Laboratory (i.e., Melton Branch Watershed), (2) apply geostatistical methods to conditionally simulate realization of input parameters at all three-dimensional gridpoints from spatially distributed field measurements, (3) develop a three-dimensional fluid flow and hydrogeochemical transport model equipped with an efficient and accurate numerical algorithm, and (4) validate the generic three-dimensional model with measured fluxes and chemical distribution from the field facility using input parameters obtained. Spatial characterization of the field site physical properties has been nearly completed in previously funded DOE initiatives (Subsurface Transport Model Validation - Jardine/Wilson/Yeh). The current research stresses the spatial characterization of chemical properties at the field facility and these include (1) soil indigenous cations and anions, (2) soil pH, (3) soil cation and anion exchange capabilities, (4) competitive electrostatic interactions, and (5) soil surface complexation reactions. Because it is not possible to make field measurements at all possible three-dimensional gridpoints for application, geostatistical techniques are used to simulate hydrologic and geochemical parameters at all three-dimensional gridpoints using the measured data. The spatially characterized experimental data are then used as input parameters for a newly developed three-dimensional fluid flow and multispecies hydrogeochemical transport model. Successful field scale modeling requires an efficient and accurate numerical algorithm, which is accomplished by modifying the Lagrangian-Eulerian approach with a peak-capture adaptive local grid refinement that greatly reduces the number of nodes and decreased the number of time-steps for discretization. The predictive capabilities of the model are compared to storm-driven multispecies solute transport studies conducted at the field facility in 1990-1991. Potential validation of the model allows engineers to develop remediation strategies for complex waste sites targeted at specific problems and with a higher probability of success. (RPIS 10502)

Department of Geosciences

679. Generation and Mobility of Radon in Soil

A.W. Rose

(814) 865-7261

\$110,000

This research determines the processes that cause large seasonal and short-term changes in the radon (Rn) content of soil gases and develops methods of predicting and modeling these variations. The relation of Rn emanation coefficients to forms of radium (Ra) and other U-series decay products—particularly the role of Ra in organic matter and iron oxides—is being evaluated. The conditions in which convection of gas in soil and bedrock may affect soil gas radon availability in houses are also being investigated. Finally, investigators are collaborating with other DOE researchers to evaluate Rn flux into houses, using well-characterized soil sites.

Detailed investigations of seasonal and short-term variability in soil gas radon are underway at several of the 13 sites previously studied in detail. Two new sites on hillsides are being used to investigate convection of soil air, and the short- and long-term variations of radon adjacent to a house are being studied. (RPIS 9663)

Physical Sciences, Inc.

Andover, MA 01810

630. An Imaging Fabry-Perot Spectrometer for Site Evaluation of Trace Species

W.J. Marinelli

(508) 689-0003

\$49,990

Field-operable analytical systems are required to evaluate potential hazardous chemical sources and to monitor remediation sites. This project is developing an imaging infrared spectrometer that can rapidly screen field sites to detect the presence of volatile organic compounds from remote locations (either in the air or on the ground). The system employs a close mirror spacing to enhance optical throughput and enable wide spectral coverage at modest resolution. Thermal emission from molecules in the fingerprint region of the spectrum (825 to 1,250 cm^{-1}) is detected against a cold atmospheric background using a mercury-cadmium-tellurium array detector. The system employs a wide field of view and hence can be used to screen large areas for emission sources with environment. Response times of 10 to 20 Hz are typical, and the response time is fundamentally limited only by the speed at which the ambient wind flushes the small sample volume. The humidity measurement technique is sufficiently stable and reliable to allow a single sensor to be used for measurements of both water vapor flux and steady-state humidity. The Phase I work plan includes laboratory and atmospheric testing of a proof-of-concept water vapor flux sensor, marine testing for investigation of potential optical window problems, and the drafting of a Phase II sensor design and Phase II work plan. This new measurement capability could make a significant contribution to DOE's overall program goals of achieving a better understanding of the ocean's role in global

climate change and the environmental consequences of energy use. While being responsive to DOE scientific program interests, this line of research could also result in a new generation of practical, cost-effective, ultrasensitive, very rugged hygrometers for the industrial sector. Industrial applications will benefit the Nation's economic competitiveness in manufacturing systems. (SBIR)

Purdue Research Foundation

West Lafayette, IN 47907

Water Resources Program

681. Supercomputer Simulation of Clay-Chemical-Water Interactions: Phase III

J.H. Cushman

(317) 494-8040

\$156,000

This research project represents a combined theoretical, experimental, and computational attack on the problem of the transport of chemical mixtures in microporous media (e.g., soil clays and rock with microfractures). Molecular scale simulations, to be carried out on Purdue and DOE supercomputers, will provide insight into the complex behavior of vicinal chemical mixtures. Theories of transport and adsorption based on rigorous statistical mechanics are being developed. Theoretical studies on the propagation of information from the microscopic to macroscopic scales are also being conducted. Experiments are being undertaken to determine diffusion coefficients between clay mineral surfaces and the related solvating fluid viscosity. These results will be compared to the computational results already mentioned. The role played by molecular size in adsorption of neutral organics is being analyzed.

The ultimate objectives of the research are to (1) develop an understanding of the molecular mechanisms controlling adsorption, desorption, partitioning between bulk and vicinal phases, and the transport of chemicals and colloids in microporous media; (2) use this information to classify DOE-generated chemicals (and their derivatives) based on the fundamental chemistry and physics of transport and transformation in natural systems; and (3) develop the linkage between molecular scale and bulk scale processes and to use this linkage to help define macroscale constitutive variables. (RPIS 10003)

Rensselaer Polytechnic Institute

Troy, NY 12181

Department of Biology

682. Phylogenetic Relationships Among Subsurface Micro-Organisms

S.A. Nierzwicki-Bauer

(518) 276-2699

\$213,000

The goals of this research are to (1) develop 16S ribosomal ribonucleic acid (rRNA)-targeted oligonucleotide probes for specific types and groups of deep subsurface micro-organisms, (2) study (with these probes) the phylogenetic relatedness of micro-organisms in different types of subsurface environments, and (3) develop probe-based methods for detecting specific subsurface microbial types without having to culture them in the laboratory. This project involves the development of group-specific, 16S rRNA-targeted oligonucleotide hybridization probes for the rapid detection of specific types of subsurface micro-organisms (e.g., groups of microbes that share certain physiological traits). Because portions of the 16S rRNA molecule are unique to particular organisms or groups, these unique sequences can serve as targets for hybridization probes with varied specificity. Target sequences for selected microbial groups are being identified by analysis of currently available rRNA sequence data for subsurface microbes. Hybridization probes are then used for these target sequences, and their effectiveness and specificity are tested. Selected probes are then being used to study phylogenetic relationships among subsurface microbes and to classify these organisms into the specific groups that the probes are designed to detect. This work is being performed first on microbes isolated from the Savannah River Site during the first phase of the Deep Microbiology Subprogram and later on microbes isolated from other DOE sites during the transitional phase. Of particular interest is the relatedness of microbes in different geological formations at each site and of microbes from different sites. The probes are also being used with in situ hybridizations to detect and monitor selected microbial groups in laboratory macrocosms and freshly collected subsurface samples. The in situ hybridizations permit detection of selected microbial types without isolating and culturing them in the laboratory. (RPIS 10262)

University of Tennessee

Knoxville, TN 37932

Center for Environmental Biotechnology

683. On-Line Monitoring of Aerobic Bioremediation with Bioluminescent Reporter Microbes

G.S. Saylor

D.C. White

(615) 675-9450

\$140,000

Engineered bacteria containing the lux gene cassette in critical operons of processes that are involved in bioremediation of mixed organic waste or immobilization of inorganic elements that are in

hand or will be created are used as reporters to monitor these critical processes as parameters of the systems are manipulated. The engineered organisms are incorporated into multispecies microbial consortia in biofilms on metallic surfaces which are simultaneously monitored electro-chemically as the nutrient composition and electron donor/acceptors are manipulated and the biodegradation of carbon-rich contaminants (toluene, benzene, xylene) and fortuitously metabolized contaminants (tri-chloroethylene and products) are monitored semicontinuously by capillary gas chromatography/mass spectrometry. The effects of these processes on the mobilization/immobilization of inorganic elements (Hg, Cr, Pb, Cu) or radioactive surrogates (Sr, Co, Cs) will also be monitored by inductively coupled plasma atomic absorption. "Reporter" bacteria with lux in naphthalene biodegradation pathways are in hand. New genetic constructs are sought in toluene or methane oxygenases involved in fortuitous degradation, in the synthesis of the endogenous storage material poly beta-hydroxy alkanoate, or the uronic acid containing extracellular polysaccharide polymers. The systems shown to be effective in biodegradation/immobilization in the flow-through microcosms are isolated in flow-through chambers which are separated from the environment. The bioluminescence in the isolation chamber is monitored remotely through a fiberoptic cable and photon counting system. These are utilized in wells or bioreactors to provide continuous in situ "reporting" for effects of manipulations of nutrients, water, and electron donors/acceptors in situ subsurface treatment systems for mixed organic/organic waste and mixed organic/inorganic wastes. (RPIS 10497)

Institute for Applied Microbiology

684. Biochemical Markers for In Situ Microbial Community Structure

D.B. Ringelberg
J.B. Guckert
T.J. Phelps
D.C. White
 (615) 675-9450

\$90,000

The goals of the research are to (1) determine and compare microbial biomass, community structure, and nutritional status in hydrochemically and hydrogeologically diverse subsurface environments and (2) identify the nutritional components that induce starvation or unbalanced growth in subsurface microbial communities. A signature biomarker technique based on phospholipid ester-linked fatty acid (PLFA) pattern analysis provides data on the total viable or potentially viable microbial communities in subsurface sediments without necessitating quantitative recovery from these sediments or the ability to culture the micro-organisms in the laboratory. This technique also provides evidence for the nutritional status (starvation or unbalanced growth) of the subsurface microflora in situ. Microbial biomass, community structure, and nutritional status in subsurface materials recovered from the Idaho National Engineering Laboratory and the Hanford Site are being determined, using PLFA analysis and related

methods. The same methods are also being applied to isolated subsurface microbial strains or consortia of strains in order to (1) determine which nutritional components are inducing starvation or unbalanced growth, (2) discover relationships between PLFA patterns and physiological groups of micro-organisms, and (3) study the distribution of PLFA biosynthetic pattern types in distinct geologic formations. Completed analysis of sediments and microbial isolates from the Savannah River Site (sampled during the first phase of the Deep Microbiology Subprogram) suggested that (1) unique classes of subsurface microbes whose existing PLFA patterns are distinctly different from those of topsoil and other microbes and (2) subsurface microbes isolated from different geological formations had distinct PLFA clustering patterns. Experiments in the transitional phase of the program are determining whether these general findings can be extended to sites that are hydrochemically and hydrogeologically distinct from the Savannah River Site. (RPIS 10266)

U.S. Geological Survey

Denver, CO 80225

685. Geohydrologic, Geologic, and Geochemical Processes Affecting Radon-222 in Groundwaters from Crystalline-Rock Aquifers

R. Wanty
E. Poeter
W. Day
P. Folger
D. Frishman
P. Briggs

(303) 236-1531

\$150,000

This project focuses on the natural processes that cause high concentrations of radon, radium, and uranium in groundwater. These radionuclides may present several problems when groundwater, especially from private wells, is used for domestic supply. Radon-222 in groundwater may degas into the indoor air, thus increasing indoor-radon levels. If present in great enough concentrations, radionuclides, such as uranium and radium, may be a direct health threat when the water is ingested. Specific objectives include evaluation the contribution of radon from water to indoor air, establishing relationships between the geology of an area and its potential to have high radon concentrations in groundwater, and exploring the relationship between groundwater flow in fractures and transport of radon in groundwater from its source within the rocks. (RPIS 10455)

U.S. Geological Survey

Reston, VA 22092

Geologic Division**686. An Investigation of the Geology and Geochemistry of Radon in Sheared and Fractured Rocks***L.C.S. Gundersen*

(703) 648-6427

\$180,000

Levels of radon progeny in houses depend largely on the geology underlying the house foundation. This study characterizes the four principal geologic terrains that cause the highest and most extensive indoor radon problems in the U.S.; predicts their national distribution; and defines the climatic and chemical processes that affect uranium and radium sitting in rocks and soils, and that ultimately affect their emanation and radon potential. Thermodynamic geochemical models are being developed, using geological and chemical analyses of radio-nuclides to understand and predict the concentration of uranium and radon in these rocks. Physical and chemical models of the soil and rock structure are being developed to explain the migration and high emanation of radon and its relation to climate and soil genesis. The chemical processes affecting the concentration of radon and its presence in ground-water continue to be evaluated.

Nine sheared granite plutons from different climatic areas across the U.S., two faulted carbonate terrains from an arid area and a humid area, and three sites within the fractured Pierre shale and the glacial deposits derived from it in the northern Great Plains have been chosen. Geological and structural mapping is being conducted across each study area, accompanied by sampling of outcrop for chemical and structural analysis. Soil profiles are being examined, accompanied by measurements of radon in soil gas and surface gamma radiation. Analyses of uranium, thorium, and their progeny elements are being made to determine geochemical models for the concentration and residence in the soil of these elements. Permeability, grain size, and radionuclide distribution are being studied to understand the emanation of radon. The development of a simple and precise emanation protocol, utilizing a soil coring device and modified Tempe cell, is an integral part of this study.

An attempt is also being made to develop a predictive radon potential tool, similar to the linear heat flow-heat production relation that resulted from earlier studies of geothermal energy in the Appalachian Mountains. The relationship between heat production, heat flow, emanation, and soil radon for several of the granite plutons in the Appalachian Mountains will be calculated. If a quantifiable relationship exists, heat production/heat flow may be extremely useful in predicting radon potential. (RPIS 9823)

687. Gas Transport in Soils and Its Relation to Radon Availability: Identifying Regional Controls of Radon Availability*G.M. Reimer*

(703) 648-6997

\$150,000

The major parameters affecting the distribution of radon in any particular geographic region are being examined to develop an assessment technique to help characterize those areas. The major factors being examined are (1) source rock type; (2) soil characteristics, including permeability; (3) soil-gas radon availability (emanation and transport); (4) climate; and (5) gamma-ray signature. The data from this project are being incorporated with those of other researchers to develop a simplified model employing the previously listed criteria and to test that model against actual field measurements. This model is not intended to replace models developed by other projects, but is using only those major parameters for which data are easily collected or available.

In addition, methods are being developed to discern the relative influence of the soil micropore and macropore regimes in controlling radon availability and to attempt development of a method to estimate in situ emanation by using soil-gas radon concentrations and down-hole ^{214}Bi measurements.

The U.S. is divided into physiographic provinces characterized by terrain (lithology) and vegetation. To a large extent, the physiography is defined, influenced, or maintained by climatic zones. By superimposing physiography and climate, distinct regions that can serve as a classification base for regional studies can be defined.

The researchers are performing detailed radon studies, on a regional scale, over a few selected areas of the country. Those regions are being chosen to represent the contrasts found among different climates, physiographies, and lithologies. For example, the country can be divided into the classical physiographic provinces of coastal plain, mountain, intermountain, interior lowlands, and high plains. Crosscutting these trends are climate regimes such as humid continental, humid subtropical, desert, steppe, and marine. The areas are geographically and geologically diverse. Studies have been initiated or compiled by other investigators in some of the areas included on this list, and the information gathered attests to the validity of the geologic-based projections. Areas representing additional climates and physiography not already studied will be selected so that regional effects on radon throughout the conterminous States can be generally represented.

Soil characteristics are being measured in various areas to evaluate their influence on the simplified model concept. Additional observations would include topographic setting and differences in vertical or horizontal migration of soil gases (done with gas injection studies). Preliminary data from helium injection experiments in soil indicate that it may be possible to resolve several pathways of migration. The pathways could have different permeabilities that are unequal in response to soil moisture—the primary short-term control of varying permeability. If the radon availability is different

for each pathway—as may be the case, because emanation can vary with grain size (and grain size distributions influence permeability)—there would be important implications for determining coupling factors for structures. (RPIS 9664)

University of Virginia

Charlottesville, VA 22903

Department of Environmental Sciences

688. The Kinetics of Aromatic-Hydrocarbon Biodegradation and Concomitant Geochemical Reactions Pertinent to Groundwater Systems

J.S. Herman

(804) 924-7761

\$100,000

Aromatic hydrocarbons are contaminants of concern in many environmental restoration projects, both alone and as mixed wastes, and are known to undergo microbial degradation under both aerobic and anaerobic conditions. These biodegradation reactions have direct impact on the geochemistry of the subsurface environment, yet this interaction is largely unquantified. The project is currently engaged in (1) a series of controlled and replicated laboratory experiments designed to examine and quantify the rates of geochemical reactions driven by aromatic-hydrocarbon biodegradation and (2) modification and use of a geochemical reaction-path model by including expressions for the reaction rates. In laboratory experiments, investigations continue in (1) the biodegradation rates of benzene, toluene, and xylene, individually and in mixtures, and (2) the resulting changes in geochemical conditions. Results from the experiments are interpreted in light of a rate model so that parameters of a rate law may be estimated and the rate law incorporated into a geochemical reaction-path model. Time-course predictions can then be made concerning the occurrence of the contaminant hydrocarbon and its impact on geochemical reactions in hypothetical hydrogeologic settings. It is anticipated that this work will (1) greatly enhance the understanding of the rate of biodegradation reactions of aromatics and of the interaction between biodegradation and other geochemical reactions in a groundwater system and (2) improve the ability to predict the behavior of aromatic hydrocarbons and associated geochemical changes in contaminated hydrogeologic systems. (RPIS 10321)

689. Factors Affecting Transport of Bacterial Cells in Porous Media

A.L. Mills

J.S. Herman

G.M. Hornberger

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\$99,000

The goal of this research is to examine and quantitatively determine the parameters that control the growth and transport of bacteria in saturated porous media. A series of laboratory experiments is being conducted using soil columns (consisting of quartz, quartz with an iron hydroxide coating, feldspar, or

mica) that have been saturated with a synthetic groundwater solution. Pore size distribution is being controlled by varying mineral grain size and distribution in uniform or unstructured patterns. Motile or nonmotile bacteria varying in size and shape are being introduced into soil columns at constant flow rates. Through a combination of labeled cells and microscopic observations, the effects of variations in transport parameters (surface chemistry, flow rate, pH, grain size, and bacterial shape and motility) on bacterial mobility and adsorption are being determined. (RPIS 10036)

Yale University

New Haven, CT 06511

Department of Geology and Geophysics

690. The Determination of ^{222}Rn Flux from Soils Based on ^{210}Pb and ^{226}Ra Disequilibrium

K.K. Turekian

(203) 436-4760

\$100,000

For radon ^{222}Rn to enter a structure, it must be generated in soil, emanate from the substrate, and migrate to the foundation. This research measures the capacity of different soils to generate and transport ^{222}Rn and relates the capacity of soils to supply ^{222}Rn to readily mappable soil properties. To assess the capacity of soils to transport ^{222}Rn to the foundations of structures, the mean flux of ^{222}Rn from undisturbed solids to the atmosphere is being determined, averaged over a period of decades. Through the sampling of a variety of soils, information on the effect of different soil properties on the escape of ^{222}Rn is gained. Estimates of the effective in situ permeability of soil are being obtained by measuring the fraction of ^{222}Rn that escapes to the atmosphere as a function of depth in the soil.

The determination of the flux of ^{222}Rn (half-life = 3.8 days) to the atmosphere from soils can be determined by measuring ^{210}Pb (half-life = 22 years) and ^{226}Ra (half-life = 1,620 years) soil samples from cores up to two meters long. With the help of direct laboratory measurements and modeling, the mean ^{222}Rn flux over 100 years can be determined at any site that has been effectively undisturbed for more than 100 years.

This sampling has been conducted extensively in the U.S. (including Hawaii and Alaska—although the results are sparse for these States). Geographical coverage is being increased so that all geologic terrains, soil types, and climates are represented. In addition, investigators are attempting to understand the mechanism for the release of radon from depths greater than 50 centimeters—mechanisms other than molecular diffusion, such as pressure-induced macropore flow; advection due to plant transpiration; or transport through plants. The role of horizontal groundwater-mediated flux of radon based on studies of salt marshes through tidal cycles as well as fresh-water wetlands is being considered. Work on radon recoil from specific sites in rocks indicates the importance of mineral surface sites for radon recoil supply. Release of radon from such surfaces, combined with the presence of advective flow along cracks and biologically mediated pathways,

may be responsible for radon loss from depths greater than 50 centimeters. The mechanisms controlling the escape of ^{222}Rn to the atmosphere also control its migration toward structures. Comparison of ^{222}Rn fluxes from different soils with each other and with model predictions allows investigators to infer information about the mechanisms responsible for ^{222}Rn transport. These mechanistic inferences can then be tested and applied to the better understanding of transport phenomena in natural soils. Such understanding will result in improved prediction and remediation of ^{222}Rn hazards. Investigators are hoping to provide a measure of the long term radon flux in a range of geographical and geologic terrains as seen in the ^{210}Pb – ^{226}Ra disequilibrium in soil profiles. A map of the U.S. showing the radon fluxes that have been measured is being prepared.

A program for direct radon flux measurements from soils and salt marshes compares short-term fluxes with the long-term estimates from ^{210}Pb – ^{226}Ra disequilibrium. (RPIS 9661)

Environmental Processes and Effects: Ecological Research

Intramural DOE Laboratories

Argonne National Laboratory Argonne, IL 60439

Environmental Research Division

691. Cooperative Support for the Fermilab National Environmental Research Park

J.D. Jastrow

(708) 252-3879

\$116,000

Fermi National Accelerator Laboratory (Fermilab) is the sixth National Environmental Research Park established by DOE. The Research Parks are protected land holdings within which ecological and environmental research and monitoring are being conducted. Collectively, the six Research Parks form the foundation of a network representing continental gradients of moisture (west-east) and temperature (north-south) that can be used to study ecological questions from regional to national scales. Fermilab is the only Research Park representing the central portion of the country. Because Fermilab's primary programmatic mission is to conduct fundamental research in high energy physics, the Fermilab National Environmental Research Park has relied upon ecological and environmental expertise from nearby Argonne National Laboratory for assistance in technical interactions with the Research Park Program (ParkNet). Argonne cooperates closely with Fermilab in ParkNet activities, especially those directed toward the cross-site coordination and networking; database management; and the analysis, synthesis, modeling, and dissemination of ecological information. (RPIS 60439)

692. Stress Tolerance Strategies in Plant/Soil Systems

R.M. Miller

(708) 252-3879

\$145,000

Roots are intimately associated with the biological activities of soils surrounding them; thus, any alteration in root activities will have a profound influence on soil processes. This influence can be via direct effects on soil biota and associated turnover and nutrient supply rates or through plant-induced changes in soil structure that affect soil physical processes and indirectly influence the biota and their habitat. Thus, an important element in predicting the consequences of energy development on plant community structure is increased understanding of how roots and associated soil biota adapt to change and how these adaptations, in turn, influence soil processes.

The research suggests that soil aggregate formation can be explained by the amount of extraradical mycorrhizal hyphae associated with the various morphologies of the plants' roots. The kinds of associations that roots have with mycorrhizal fungi also appear to be related to plant lifeform and habitat. These findings are used to develop a hierarchical model of the influence of plants on soil structure. Substantiation of this model leads to better understanding of the interrelationships of lifeform, belowground community structure, soil structure, and soil processes. Hence, the model is a valuable tool for extending the interpretation of biotic processes to higher levels of organization. (RPIS 4414)

Fermi National Accelerator Laboratory Batavia, IL 60510

Fermilab MS 119

693. Fermilab National Environmental Research Park

R. Walton

(708) 840-2565

\$50,000

All environmental research at Fermilab is provided by outside investigators using their own funds. A major task of the Fermilab National Environmental Research Park is to provide support to these investigators. Examples of support provided are purchase of computer hardware and software, purchase of materials necessary to provide researchers with adequate experimental setups (such as fenceposts, netting, fencing, or marking and monitoring equipment, and purchase and setup of a meteorological station. A botanist hired with program funds is initiating an ongoing survey of the prairie restoration project at Fermilab. This intensive survey will be carried out annually to establish a baseline characterization of the prairie ecosystem at Fermilab and to monitor ongoing changes resulting from natural succession and/or imposed stresses. In addition, a long term experiment involving the establishment of 300 acres of grassland succession plots has been inaugurated. This project requires purchasing roughly \$5,000 worth of quality controlled native seedstock every other year for the next 20 years and obtaining the labor necessary to plant the experimental tracts.

The National Environmental Research Park Program funds Argonne National Laboratory to provide technical assistance to the Fermilab National Environmental Research Park. Argonne's tasks have included preparing a comprehensive description of the site's environmental resources (including a detailed summary and history of the site's Prairie Project), developing the site's Research Park Plan, drafting a research philosophy document for the Park, creating and manipulating site databases, serving as representatives of the site at National Research Park Program planning meetings and workshops, and interacting with the Fermilab Environmental Advisory Committee and the Prairie Committee. Because the Fermilab Research Park does not have the history of environmental research that other Research Parks have, current efforts are being made to create and maintain a database to characterize the plant/soil community of existing site prairie reconstructions, to annually measure (since 1985) aboveground standing crop in the reconstructed prairie, and to conduct a cross-site study of nitrogen limitation in prairie in collaboration with the Konza LTER site. (RPIS 4820)

Idaho National Engineering Laboratory Idaho Falls, ID 83415

Radiological and Environmental Sciences Center

694. Planning Guide to Long-Term Ecological Monitoring for Global Change at DOE Research Parks

D. Bruns

(208) 526-0816

\$130,000

The objective of the work is to develop a planning guide for long-term ecological monitoring of global change at a network of DOE Research Parks. Initial efforts focus on integration of existing Research Park data with a communications network for cross-site continental and global trend analyses. The planning guide on long-term ecological monitoring for global change based on a systems conceptual framework (Wiersma 1985, Wiersma and Otis 1986, Bruns and Wiersma 1988), past monitoring activities at the Research Parks, and existing capabilities at the DOE sites. The guide develops criteria and makes recommendations in regard to: (1) selection of consistent monitoring site locations within the DOE Research Park network, (2) a set of consistent basic ecological parameters (biotic and abiotic) for long-term continental and global monitoring, and (3) steps to be taken toward initiation of the network.

The objective of the subtask on ParkNet Facilitation is to coordinate the overall team efforts of ParkNet, focusing in cross-park synthesis and analysis. These syntheses also include data from other research facilities when available and appropriate. Although much of the work of ParkNet focuses on problems related to global climate change and its effects on changing ecological systems, many other environmental questions also are addressed. All objectives focus on the development of ParkNet as a major DOE resource to address environmental problems associated with energy development and use, policy, and management technology. (RPIS 5281)

695. INEL National Environmental Research Park

O.D. Markham

(208) 526-2164

\$120,000

The Research Park cooperates with other research parks, particularly those in the west, to provide data for intersite comparisons and interpretation of ecological issues of regional and global importance. The Research Park participates in ParkNet workshops and contributes to the products (i.e. publications and presentations) resulting from them. The Research Park hosts a workshop for cross-site synthesis of long-term small mammal or breeding bird data sets. Reviews of the ecology and radioecology of the Idaho National Engineering Laboratory (INEL) are integrated, synthesized, and published. Data on the biotic and abiotic factors associated with the storage of low-level wastes on the INEL is consolidated in one volume. One document consolidates the information on all threatened, endangered, candidate, and proposed for listing species on the INEL. Efforts continue to computerize historical data bases in a uniform ParkNet format for intersite analyses. Publication of long-term data sets on small mammal population fluctuations is supported. (RPIS 0983)

Los Alamos National Laboratory

Los Alamos, NM 87545

Environmental Sciences Division

696. Los Alamos National Environmental Research Park

F.J. Barnes

(505) 667-4933

\$100,000

The Los Alamos National Environmental Research Park (Research Park) is an outdoor laboratory for conducting environmental research to further basic understanding of ecosystem structure and function under various conditions of stress and to develop advanced concepts and supporting technology to further national environmental goals. While the Research Park is not a stand-alone research project, it is host to a rich mix of basic and applied environmental research programs based in various groups at Los Alamos National Laboratory and among several universities and organizations in its network of collaborators. Funding for these programs comes from many sources including several Federal, state, and private organizations. Consequently, the mix of research programs and participants changes as funding sources change. While the basic mission of the Research Park remains constant from year to year, the changing mix of programs insures that the support research is relevant to evolving national environmental priorities. Furthermore, the strong basic science component to all of the research not only contributes fundamental understanding of ecosystem structure and function but also helps to address applied problems from a sound theoretical basis.

The focus of current activities is to promote and facilitate cross-site analyses with other ParkNet and Long-Term Ecological Research sites. This effort is supported by

continued development and updating of the ParkNet databases, bringing a Geographical Information System system online, and promoting model development and scaling studies. (RPIS 927)

Life Sciences Division

697. Plant Physiology

P.J. Jackson

(505) 667-2775

\$241,000

Different mechanisms of metal-tolerance in plants are being investigated. Tolerance to supra-optimal concentrations of certain metals results from a variety of mechanisms. Cd-tolerance occurs, in part, because plants produce large amounts of poly(γ -glutamylcysteinyl)glycine, (γ -EC) $_n$ G. The biosynthetic pathway for synthesis of this peptide requires glutathione and its precursors and includes a final condensation of two or more glutathione molecules. The substrate for the transpeptidase that catalyzes this reaction may be a metal:glutathione complex. Polypeptide complexes also contain Fe. Plants contain genes encoding metallothionein-like proteins. However, the patterns of expression of these genes are complex, and it is unknown whether the proteins encoded by these genes function in metal-tolerance or trace metal homeostasis. Many metal ions are chelated to different sites on the primary plant cell wall. Ag, Ba, Be, Cd, Cu, Eu, Fe, Gd, Ni, Pb, Pu, Sr, and UO₂ binding have been demonstrated. Luminescence studies have identified multiple binding sites for several different ions. Chelation of metal ions can also be salt- and temperature-dependent and binding is not simply the result of the ion exchange properties of the cell walls. Experiments that concentrate metal ions out of laboratory waste solutions have demonstrated the utility of plant cell walls and immobilized metal binding polypeptides for the removal of certain toxic metal ions from waste solutions. Irreversible binding of Pu and certain other ions may also be useful for the removal of trace amounts of this material from waste effluent. Plant cells actively take up and chemically modify certain explosive organic molecules (i.e., TNT, RDX, and HMX). The process of chemical modification of TNT has been partially characterized. (RPIS 4666)

Space and Science Technology Division

698. Application of a Solar-Blind LIDAR for Atmospheric and Ecological Studies

D.I. Cooper

W.E. Eichinger

J.J. Tiee

(505) 667-6502

\$250,000

The objective for the proposed research is to field LIDAR system for noninvasive measurement of three-dimensional water vapor concentrations in the near-ground atmosphere. Software is being developed for rapid correlation analysis of successive time scans, estimation of vertical and horizontal wind speeds, identification of eddies, and the calculation of water vapor

fluxes. The near real-time graphical displays of data are capable of converting the individual LIDAR returns into user-selected horizontal and vertical slices of the three-dimensional data arrays. An intensive study of a natural woodland site demonstrates the capacity of the LIDAR system for accurately measuring the spatial and temporal variability in evapotranspiration rates from mixed canopies of patchy vegetation as well as the interactions between the atmosphere and the plant canopy. (RPIS 5078)

Oak Ridge National Laboratory

Oak Ridge, TN 37831

Environmental Sciences Division

699. System Processes in Landscape Ecology

R.H. Gardner

R.V. O'Neill

M.G. Turner

(615) 574-7369

\$275,000

This project develops and uses new theoretical methods to analyze landscapes and regions where DOE must consider energy-related issues that transcend many land-use, landcover, and landownership patterns. The number and magnitude of broad-scale, energy-related questions result in the emergence of environmental properties at the regional scale, which are not detectable by traditional site-specific studies. These properties involve spatial heterogeneity and the patterning of ecological systems (e.g., vegetation) on the landscape. The spatial pattern relates directly to environmental quality and stability of ecological systems and may be altered by energy development and use. Sets of parameters have been identified that can be used to quantify these broad-scale patterns. These parameters are used in models designed to estimate landscape pattern change. Use of a suite of models and scales of landscape resolution enables the study of how changes in the patterning of ecological systems affect total system stability. The models organize information from laboratory and site studies to the landscape scale and examine the applicability of extrapolating information from one site to another. (RPIS 607)

700. Walker Branch Watershed Project

M.A. Huston

C.T. Garten

P.J. Mulholland

(615) 576-8001

\$1,270,000

The Walker Branch Watershed Project uses an experimental approach and state-of-the-art analytic methods to detect ecosystem responses to anthropogenic and natural stresses and to predict the consequences of these stresses for ecosystem productivity and sustainability. The Walker Branch Climate Change Experiment evaluates the effect of altered rainfall amounts on an upland oak forest ecosystem. This unique experimental facility intercepts and transfers 25 percent of incoming precipitation to simultaneously produce drought

conditions on one large forest plot and above normal precipitation on a nearby plot. Ecosystem processes being monitored include carbon storage and fluxes, other trace gas fluxes, tree growth and productivity, and soil biogeochemistry and hydrology. Methodologies used on Walker Branch include stable isotope concentration ratios by mass spectrometry, real-time gas fluxes by infrared gas analysis, gas chromatography and Fourier transform infrared, low detection limit spectrophotometry for stream chemistry, and elemental composition by laser ablation mass spectrometry. The 25-year long-term database of stream hydrology, precipitation chemistry, and forest growth is continued in support of DOE's local, regional, and global research and environmental restoration priorities. Monitoring and experimental data are integrated using advanced Geographical Information System technologies and computer simulation modeling. (RPIS 4877)

701. National Environmental Research Park

P.D. Parr

(615) 576-8123

\$100,000

Oak Ridge National Environmental Research Park, designated in 1980, is one of seven DOE National Environmental Research Parks. Major objectives of a National Environmental Research Park identified in the Charter are to (1) develop methods for continuous and quantitative assessment of human activities on the environment, (2) develop models to predict the response of environmental components to proposed technological activities, and (3) provide land-use plans that make preservation of representative regional natural areas compatible with human technological activities. ParkNet, a network of the Research Parks, helps integrate and synthesize data obtained through site characterization and monitoring across the parks. Cross-site data synthesis and scientific interactions that demonstrate the coordinated network of the Research Parks are emphasized. (RPIS 929)

702. Radionuclides in the Coastal Zone

K.L. Von Damm

I.L. Larsen

J.M. Grebmeier

(615) 576-0427

\$100,000

The purpose of this project is to measure naturally and artificially occurring radionuclides and to use them to understand biogeochemical processes occurring at the continent-ocean interface. The research is focused on short (months) and long (tens of years) sediment deposition and remobilization and how these processes affect the fate of energy-related materials. Significant accomplishments during the past year include: (1) preparation or publication of two papers and two abstracts related to the use and fate of radionuclides, trace metals, and carbon isotopes in the Savannah River Estuary, Chesapeake Bay, and Prince William Sound, Alaska, (2) the use of ^7Be to study areas of recent sediment deposition in Prince William Sound, Alaska and in the northern Bering Sea, and (3) analysis of sediment sampled from several stations in the Savannah

River Estuary to continue the use of ^7Be , ^{210}Pb , and ^{137}Cs as tracers of sediment resuspension and source just prior to and just after Hurricane Hugo. The project continues to quantify sedimentary processes occurring in the coastal zone in cooperation with other scientists in the DOE/OHER Marine Program as well as with those at other institutions. (RPIS 2528)

Pacific Northwest Laboratory

Richland, WA 99352

Environmental Science Research Center

703. Dynamics of Arid Land Ecosystems

L.E. Rogers

(509) 376-8256

\$350,000

This research focuses on developing and making use of measures of ecosystem adjustment that can resolve and predict anticipated changes with arid land ecosystems. The scientific community is expected to quantitatively assess the response of natural systems to a variety of natural and human-related stresses up to and including global climate change. The biological processes that control the flux of biogenic gases (CO_2 , H_2O , CH_4 , and several nitrogen, sulfur, and non-methane hydrocarbon gases) form one of the largest unknowns at the present time and a central theme for this research. The dynamics of soil nutrients, water, and energy are being studied as a basis for understanding the mechanisms with which an ecosystem controls the processing of essential resources and how these processes respond to stress. Preliminary integrative models are being developed to provide new perspectives for testing and resolving environmental problems and to eventually provide estimates of fundamental ecological properties over landscape-sized areas. (RPIS 618)

704. Environmental Research Park

L.E. Rogers

(509) 376-8256

\$100,000

Seven U.S. DOE National Research Parks are located in major ecoregions across the country, including creosote bush desert, tall grass prairie, pinyon-juniper scrub forests, oak-hickory forests, and southern pine and mixed deciduous forests. The Environmental Research Park described here is located on DOE's Hanford Site in the semiarid shrub-steppe ecoregion of eastern Washington State. The Park consists of 1,450 km^2 of mostly undeveloped land surrounded by cultivated fields and urban areas. The Columbia River flows through the Park for approximately 80 km. Nuclear materials production has ceased after 45 years of nearly continuous activity. Future activities are expected to be aimed at cleanup of contaminated soil, surface waters, and groundwater; site restoration; and environmental monitoring of the effectiveness of cleanup. Research is centered upon an evaluation and interpretation of existing environmental data with emphasis on developing quantitative inter-park comparisons. This objective is expedited through workshops on specific topics. Efforts to

expand the data management capabilities have been emphasized. Protocols for archiving ecological data sets were established and an inventory of Hanford-based data sets was completed. (RPIS 1261)

705. Designs for Environmental Field Studies

J.M. Thomas

(509) 376-7982

\$150,000

Approaches to the study of field problems in ecology are limited by the lack of theory and suitable designs for sampling contaminants and populations in time and space. This program provides a firm scientific basis for field studies to define the consequences of landscape level events, the environmental behavior of energy-induced chemicals, and their effects on populations. The research places strong emphasis on developing field designs based on clear objectives, approaches that incorporate sampling theory rather than classical experimental designs, and quantitative issues in the use of modern technology (e.g., satellite imagery to study landscape-level scales) applicable to global problems. The research is developing suitable sampling designs based on appropriate objectives for field work. Suitable designs for several classes of sampling have already been developed in other fields but are largely unknown to ecologists and environmental scientists. Hence, one part of the research is devoted to adapting results from these other fields for use in ecological studies. Investigations include replicated experiments, unreplicated experiments, intervention analysis, survey sampling, analytical sampling, observational studies, sampling for pattern, and sampling for modeling. Current emphasis is on sampling for pattern and observational studies. (RPIS 4633)

Savannah River Ecology Laboratory

Aiken, SC 29802

706. National Environmental Research Park

M.H. Smith

(803) 725-2472

\$100,000

Several data synthesis projects are currently in operation at the Savannah River Ecology Laboratory (SREL). The data archiving program has been very successful and the synthesis of past and ongoing research data sets is well underway. The archiving program is currently exploring new avenues for the collection and archiving of research documents in order to facilitate the location and rapid dispensation of vital information to DOE and scientists at SREL. The data archiving program increases the availability of information to DOE and scientists within this and other research park sites.

Scientists at SREL are involved in several specific studies involving synthesis of data relative to research issues on the Savannah River Site (SRS). One example of such research is the investigation of procedures for exploring density-dependent processes in ungulates. Results of a recent workshop that focused on density dependence in ungulates have proven to be statistically complex, and researchers at SREL are exploring

mathematical and computer models to determine the proper methods for analysis of density-dependent processes. Researchers at SREL are also in the process of gathering information relative to reproduction in white-tailed deer across North America. A synthesis of the available information of reproductive parameters in ungulates is used to better understand the productivity of deer on the SRS and results in several publications. (RPIS 2217)

Environmental Processes and Effects: Ecological Research

Offsite Grants

University of Alaska, Fairbanks

Fairbanks, AK 99775

Institute of Arctic Biology

707. Controls Over Nutrients Flow Through Plants and Microbes in Arctic Tundra

J. Schimel

(907) 474-7682

\$30,000

Labeling studies of ^{15}N have demonstrated that microbes are effective in immobilizing inorganic N and that plants get relatively little of this N tracer when it is added to the soil. At the same time, growth-chamber experiments show that *Eriophorum*, the dominant sedge of tussock tundra, can absorb and grow on amino acids as its sole source of N. On the basis of amino acid concentrations and kinetics of uptake measured in the field, it is estimated that *Eriophorum* must absorb at least half of its N as amino acids rather than as inorganic N. If this is true, it means that *Eriophorum* is short-circuiting the traditional pathways of N cycling that require N mineralization prior to plant uptake. This would require a different model structure to simulate patterns of nutrient cycling and production in tundra.

The research includes adding doubly labeled amino acids (^{14}C and ^{15}N) to tundra soils and measuring incorporation into plants and microbes. These results are compared to measurements where N is added as ^{15}N -ammonium. Results of the field uptake measurements are incorporated into the model of inorganic and organic N by plants and microbes. (RPIS 10296)

Institute of Northern Engineering**708. Arctic Hydrology and Meteorology***D.L. Kane*

(907) 474-7808

\$155,000

The human impact on the environment is increasing with time. The response and resilience of an ecosystem to such disturbances can range between subtle and striking. Usually on a macro scale (Arctic haze and climate warming), such impacts are subtle, and decades are required before significant responses are observed. On the microscale (oil spills, local destruction of surface vegetation), the impact is immediate and readily apparent within 1 or 2 years. Mesoscale disturbances can be wide-ranging; some impacts are immediately apparent (construction of roads and pipelines), others are not as obvious (dust from roads). The recovery of an arctic ecosystem from microscale disturbances, such as the removal of vegetation, can take many decades by natural processes.

This project is concentrating on a strong program of data collection, both hydrologic and meteorologic, to better understand dominant physical processes. Detailed computer programs are being developed to model physical processes occurring under the present conditions and to simulate processes under the influence of climatic change. To detect subtle anthropogenic-induced changes in the arctic environment, it is necessary to maintain continuous data collection of climatologic and hydrologic information. Continuous data collection of process-oriented studies coupled with detailed computer simulations are necessary to detect climatic change. Field research focuses on determining the natural annual and diurnal variability of climatic and hydrologic variables, especially those that may indicate trends in climatic change. (RPIS 10696)

709. Carbon and Nitrogen Isotope Studies in an Arctic Ecosystem*D.M. Schell*

(907) 474-7115

\$65,000

Using stable and radioisotope techniques, the research assesses the fluxes of carbon and nitrogen within the ecosystem, focusing on the mobilization of subfossil carbon and implications for long-term carbon storage/loss from the tundra. Tundra in the foothills is not accumulating carbon except in valley bottoms and wet lowlands. Coastal plain tundra is still accumulating carbon, but the rate has dropped in the last few thousand years. Carbon export from watersheds in the Kuparuk and Imnavait Creek drainages exceed that expected from estimated primary production. Nitrogen isotope abundances vary between species of plants and along hydrologic gradients. (RPIS 9304)

University of California, Berkeley

Berkeley, CA 94720

Department of Integrative Biology**710. Controls Over Nutrients Flow Through Plants and Microbes in Arctic Tundra***F.S. Chapin, III*

(510) 642-1003

\$30,000

Research continues to probe the effects of disturbance on nutrient dynamics and microbial activity in the arctic tundra. In particular, the dynamics of nitrogen, a critical nutrient, continue to be investigated. Data collected from this research is critically needed for complete validation of the decomposition component for the nutrient transport model. The ^{15}N labeling studies conducted in 1991 have shown that microbes are extremely effective in immobilizing inorganic nitrogen and that plants get relatively little of the ^{15}N tracer when it is added to the soil. At the same time, growth chamber experiments indicate that *Eriophorum*, the dominant sedge of tussock tundra, can absorb and grow on amino acids as its sole source of nitrogen. It appears that amino acids make up at least 50 percent of the nitrogen source for *Eriophorum* in the field. If this is the case, *Eriophorum* is short-circuiting the traditional pathways of accessing nitrogen, mineralization prior to plant uptake. Such a process requires a rather different model definition to simulate patterns of nutrient cycling and transport in the arctic tundra. (RPIS 10299)

**University of California, Los Angeles,
Laboratory of Biomedical and
Environmental Sciences**

Los Angeles, CA 90024

Environmental Sciences Division**711. Environmental Productivity Indices and Productivity for Desert Crassulacean Acid Metabolism Plants***P.S. Nobel*

(213) 825-3395

\$344,000

Indices ranging from zero to unity have been devised to quantify influences of environmental factors on the net CO_2 uptake, and hence productivity, of various crassulacean acid metabolism (CAM) succulents from arid and semiarid regions. These indices include a water index, a temperature index, and a photosynthetically active radiation (PAR) index. Based on the effects of water status, temperature, and PAR on net CO_2 uptake measured over 24-hour periods in the laboratory, the three indices for water, temperature, and radiation can be determined daily, using values of the appropriate environmental parameters at a particular field site. The product of the three indices, known as the Environmental Productivity Index (EPI), indicates the relative CO_2 uptake ability under a particular set of environmental conditions. A nutrient index, similarly ranging

from 0.00 to 1.00, has also been proposed to quantify the influence of soil element levels on shoot CO_2 uptake. EPI can predict the productivity of various agaves and cacti over wide geographical areas. For instance, productivity for *Opuntia ficus-indica* has been predicted for 253 regions within 60° of the Equator, using data from 1,464 weather stations. For a canopy of closely spaced plants, predicted productivities were at least 10 metric tons (dry weight) $\text{hectare}^{-1} \text{year}^{-1}$ for nearly half of the Earth's land area. EPI and the measured response of CAM plants to elevated CO_2 levels can also be used to predict the productivity of *O. ficus-indica* on a worldwide basis for rainfall patterns, temperature changes, and PAR conditions resulting from various anthropogenic environmental changes that are predicted for the future. (RPIS 9263)

University of Colorado

Boulder, CO 80309

Institute of Arctic and Alpine Research

712. Landscape Dynamics in the Arctic Foothills: Landscape Evolution and Vegetation Succession on Disturbances

D.A. Walker

(303) 492-7303

\$110,000

This is the continuation of the Landscape Dynamics project as part of DOE's R4D (Response, Resistance, and Resilience to and Recovery from Disturbance) Program. The project contains two major components: Subproject I, Landscape Evolution: Geobotanical Mapping and Terrain Analysis, and Subproject II, Community Dynamics and Recovery Following Disturbance. The extension is needed to finish work proposed for 1991. Specifically, it is for (1) analyzing the Toolik Lake permanent plot database; and (2) writing three chapters for the synthesis book for the R4D project and six papers for journals.

Three chapters have been written and submitted for publication in the book *Landscape Function: Implication for Ecosystem Response to Disturbance—A Case Study in Arctic Tundra*. The chapters are currently being revised. The titles of the chapters are "Hierarchy of Disturbance in Alaskan Arctic Vegetation," "Site Description of the R4D Research Site Using a Hierarchical GIS," and "Vegetation and Soils of the Imnavait Creek Site." (RPIS 9294)

Colorado State University

Fort Collins, CO 80523

Natural Resource Ecology Laboratory

713. Grassland/Atmospheric Response to Climate Change: Coupling Regional and Local Scales

M.B. Coughenour

(303) 491-5572

\$70,000

Predicting the impact of global changes in climate and CO_2 on ecosystem processes is a formidable task facing ecologists. This problem requires understanding complex interactions among atmospheric and ecological processes operating on different scales. This problem is addressed with a hierarchical modeling approach. A regional and mesoscale atmospheric model is used to interpret global circulation model results at regional and finer scales. A newly developed protocol for hierarchical information exchange between high and low temporal resolution physiological and soil process models simulates multilevel and multiscale ecological response to CO_2 and climate change. Finally, these models are used in a set of modeling experiments that demonstrate their utility in predicting ecosystem and atmospheric impacts of climate and CO_2 change at multiple spatial and temporal scales for the North American Central Grasslands. (RPIS 10181)

Duke University

Durham, NC 27706

Department of Botany

714. Effects of Disturbances on Ecosystem Dynamics of Tundra and Riparian Vegetation

J.F. Reynolds

(919) 684-3715

\$195,000

This work involves model development and variation that builds on models already developed and being developed and on a substantial body of field research on plant and ecosystem processes in tundra. This researcher and a researcher from the University of California at Berkeley, who has worked in the Arctic for many years and offers extensive research experience in arctic ecosystems, have been closely collaborating in arctic research for the last 2 years.

This Response, Resistance, and Resilience to and Recovery from Disturbance modeling is guided by a general framework that can be stated as a central hypothesis: "Energy-related disturbances (e.g., climate change and road building) have their greatest effect on arctic ecosystems through effects on soils processes that alter nutrient availability, nutrient uptake by the vegetation, and nutrient transport from the ecosystem." This framework is important because it commits us to understanding the ecosystem linkages, feedbacks, and time lags between soils and plants rather than just focusing on the direct effects of disturbances on vegetation. Modeling is the most efficient way to explore the possible linkages, feedbacks, and time lags in the soil-plant system.

This project developed and published most of the modules that comprise the General Arctic Simulator (GAS), a mechanistic, patch level ecosystem model of tussock tundra: e.g., plant growth and development, gas exchange, nutrient uptake, decomposition, freezing and thawing of permafrost, etc. Although each model has been developed independently, the links between models have been considered in their development. During the next year, one objective is to link these modules into a functional GAS. Preliminary linking of GAS and the terrain hydrology simulator to form the Arctic Landscape Simulator (ALS) is also a goal. ALS considers the spatial distribution of biotic communities on a landscape as well as the fundamental processes that occur at the patch and transport levels. ALS explores linkages among communities to determine whether important interactions among communities are linked by water flow. The major questions addressed here are whether nutrient uptake or loss or storage of water by a given community have a major influence on downstream communities. This question must be addressed before patch scale processes can be extrapolated to larger spatial scales. (RPIS 10710)

Ohio State University Research Foundation Columbus, OH 43212

Byrd Polar Research Center

715. Hydrological and Geochemical Response and Recovery in Disturbed Arctic Ecosystems

K.R. Everett

(614) 292-6531

\$93,000

This work is significant because it is the first detailed study of the hydrology and geochemistry of a moderate sized, well-defined Arctic drainage basin and its subbasins. Within the framework of the Response, Resistance and Resilience to, and Recovery of Arctic Ecosystem to Disturbances (R4D) program, the research provides baseline data upon which to judge the response of the basin and its subbasins to chemical and physical perturbation. In conjunction with a number of other R4D studies the project contributes input to several process-response models of the basin as a whole and of the catchment slopes. (RPIS 9286)

Princeton University Princeton, NJ 08544

Department of Ecology and Evolutionary Biology

716. A Theory of Forest Dynamics: Spatially Explicit Models and Issues of Scale

S.W. Pacala

(609) 258-3870

\$60,000

This research is empirically calibrating and testing a theory of forest dynamics that encompasses a broad range of spatial and temporal scales. The research consists of an integrated program of computer and mathematical modeling together with empirical studies of 12 forest tree species that are canopy dominants in transitional oak-northern hardwoods forests. The empirical studies provide the data necessary to explicitly calibrate spatial models of forested landscapes that include the following characteristics: (1) competition for light, water, and mineral nutrients, (2) dispersal, (3) disturbance, (4) soil and topographic heterogeneity, and (5) patterns of forest fragmentation. The models should be applicable to landscapes as large as 10^4 to 10^5 km² and yet should retain fine scale resolution important to single individuals. The models are designed so they can be tailored to forecast the consequences of energy-related and other anthropogenic perturbations such as acid rain, elevated CO₂, and ultraviolet radiation, and global warming. (RPIS 10715)

Stanford University Stanford, CA 94305

Hopkins Marine Station

717. Theoretical Ecology of Marine Populations

J. Roughgarden

(415) 723-3648

\$93,000

This project developed and is testing mathematical models that predict demographic change in an open population with space-limited recruitment, such as the change in marine organisms with a sessile adult phase and a pelagic larval phase. The composition of barnacle-dominated communities in the intertidal zone of central California in the vicinity of Hopkins Marine Station is controlled by the rate of arrival of larvae at potential sites. Processes that act after larvae arrive, such as predation and crowding, are of secondary importance. This project focuses on developing mathematical models for a species population consisting of (1) sessile adults distributed among heterogeneous space-limited benthic habitats and (2) larvae in the surrounding water mass. These models treat the evolution of marine life histories and the conditions for regional coexistence of marine species. The research is also studying the influence of predation on barnacle larvae by juvenile fish that live in offshore kelp forests. The kelp forest community is coupled to the intertidal community because kelp affects the rates of arrival of the larvae from intertidal organisms. (RPIS 9408)

University of Utah Salt Lake City, UT 84112

Department of Biology

718. Water Use, Productivity, and Interactions Among Desert Plants: Vertical Integration Using Stable Isotope Ratios

J.R. Ehleringer

(801) 581-7623

\$347,000

Water is recognized as the primary factor limiting productivity and influencing community composition in deserts. The objectives of this research are to gain insights into (1) how variation in gas exchange characteristics at the leaf level translates into dry matter production in aridlands and (2) the role of both intra- and inter-specific variation in the mechanistic aspects of water use in structuring aridland communities and ecosystems. A primary goal of the research is to determine the extent to which long-term integration of physiological processes at the individual and species levels is reflected in the stable isotopic composition of biological materials. If this linkage can be established, as is strongly suggested by preliminary data, then it will provide a conceptual and theoretical framework with which to predict the consequences of changes in climatic conditions or disturbance on the nature of community dynamics. If ecology is to eventually predict the consequences of environmental change on ecosystem dynamics, then tools will be needed that allow process level observations to be made and scaled to the ecosystem level. Stable isotopic analyses at natural abundance levels are likely to be useful tools in this endeavor. (RPIS 9972)

University of Wisconsin Madison, WI 53706

Department of Zoology

719. Physiological and Ecological Implications of Coupled Heat-and-Water-Transport Mechanisms of Endotherms and Vegetation

W.P. Porter

(608) 262-1719

\$221,000

Models can quantitatively predict effects of environmental change on animal growth and reproduction. This research develops general models of food, water, and heat balances for ectotherms and endotherms and tests predictions for a wide range of species in various environments. This project thus, identifies and quantifies important interactions between climate, physiology, and behavior in animal growth and reproduction. The research focuses on three activities. (1) It extends a current recently developed quantitative, general heat-and-water-transfer model intended for the porous insulation of endotherms to include the porous media of vegetation. (2) It tests the model's predictions for endotherm heat-generation requirements and water-loss rates for different insulations under conditions measured in the laboratory and in the field on various inanimate objects and live endotherms.

(3) It integrates the porous media model with microclimate models already field tested in many environments to calculate heat and mass fluxes through low canopies of vegetation and the soil. The mechanistic model for endotherms will ultimately provide an enhanced means for generating and testing ecological hypotheses, such as environmental effects on herbivory rates, growth and reproduction rates, survival probabilities, and population dynamics. (RPIS 9790)

Global Change: Climate Modeling and CHAMMP

Intramural DOE Laboratories

Argonne National Laboratory Argonne, IL 60439

Mathematics and Computer Sciences Division

720. Parallel Atmospheric Climate Model

I.T. Foster

(708) 972-4617

\$520,000

This project provides technological advances in numerical methods and parallel processing to support the modeling of the atmospheric component of the climate system on advanced computing architectures (i.e., massively parallel computers). An interdisciplinary team is being established at each of three national research institutions: Argonne National Laboratory, Oak Ridge National Laboratory, and the National Center for Atmospheric Research (NCAR). At these centers, research activity is being conducted in three related categories: advanced numerical methods, model development, and parallel software tools. Specifically, new methods, large scale testbeds and parallel software tools are being developed in three distinct, but closely integrated subprojects. The focus of the first subproject is the development and evaluation of both parallel algorithms for existing numerical methods and new methods and algorithms suitable for large scale parallel climate models. Prototype implementations of methods and algorithms applied to the shallow water equations on the sphere are used to study accuracy, efficiency, and suitability for massively parallel execution. The second subproject consists of an investigation of an existing climate model [NCAR Community Climate Model Two (CCM2)] with the intention of developing a usable parallel implementation for distributed-memory multiple instruction, multiple data computers. Parallel algorithms and promising new methods developed in the first subproject, as well as techniques for including new model physics, are incorporated into the parallelized CCM2 for further evaluation. The third subproject is concerned with the design and development of parallel software techniques and tools to support algorithm development. These tools are intended to support the archiving of expertise developed in the project and the performance evaluation and characterization of large scale parallel codes. (RPIS 5373)

Brookhaven National Laboratory Upton, NY 11973

Department of Applied Sciences

721. Loosely Coupled Distributed Modeling of Climate Change

H.B. Stewart

(516) 282-4179

\$150,000

This projects entail developing methods of running coupled submodels of advanced climate models (ACMs) simultaneously on separate processors. The project approach explores the hypothesis that the modeling of climate systems can be decomposed to treat different processes coupled only loosely in time-i.e., the exchange of information among processes need not be strictly constrained in phase. Such asynchronous coupling allows exploration of alternative computing approaches. Three computing environments are being explored. The environments are (1) shared memory multiprocessor systems (e.g., IBM3090/x00, Cray X/MP); (2) heterogeneous computers linked by a local area network; and (3) geographically separate, network-connected supercomputers. Tests are performed using two kinds of prototype models. Highly parameterized models of the atmosphere, ocean, sea ice, chemical constituents, ecosystems, etc., are run in a coupled mode to test constraints resulting from intrinsic time structure of the various subsystems and the interaction of multiple subsystems. Detailed regional atmospheric and ocean basin models define data transfer requirements. Final testing utilizes full scale atmospheric and oceanic circulation models. The evaluation compares traditional climate variables such as the seasonal and latitudinal dependence of temperature as well as various fluxes to expose differences in any compensating errors. The end products of this project are techniques that allow the power of physically separated computers to be harnessed for a single model computation. These techniques should alleviate some of the serious software problems inherent in building large, complex climate models. (RPIS 5375)

Lawrence Livermore National Laboratory Livermore, CA 94550

Atmospheric and Geophysical Sciences Division

722. Climate Systems Modeling on Massively Parallel Computers I: Global Ocean Circulation Model

W.P. Dannevik

(415) 422-3132

\$450,000

The project objective is to determine the degree to which advanced climate modeling efforts may benefit from current trends in the field of massively parallel supercomputing. The project is enabling the transfer of a highly vectorized ocean global climate model running on a multiprocessor CRAY

computer to a massively parallel computer (MPC) and the coupling of an MPC with an atmospheric model.

The process is achieved by first porting an existing global, high resolution, primitive equation ocean circulation model onto the Lawrence Livermore National Laboratory MPC; the model of Semtner and Chervin, presently designed for vectorization on longitude and limited parallelization on latitude, has been identified for this purpose. The project then evaluates the sensitivity of alternative data management strategies and physics package algorithm selections in such a model with respect to issues of communications latency tolerance, load balancing, and cache/local/global memory allocation on the MPC. The project also optimizes model design elements with regard to parallel scaling properties for the case in which the number of available processor elements becomes very large and assesses the developed strategies for transfer to coupled atmosphere-ocean climate design efforts. (RPIS 5337)

723. Climate Model Diagnosis and Intercomparison

W.L. Gates

(415) 422-7627

\$3,990,000

The goal of the Program for Climate Model Diagnosis and Intercomparison (PCMDI) is to better understand (and eventually to reduce) differences among climate model estimates of the regional CO₂-induced climate changes. By concentrating on the diagnostic analysis of model simulations, by providing a vehicle for communication among modeling groups, and by exploring the sensitivity of models to different resolutions, numerical methods, and representations of important processes, PCMDI provides a systematic basis for the improvement of general circulation models (GCMs). The provision of a coordinated and centralized program in model diagnosis also permits the study of a greater number of model attributes, including variables of particular interest to those studying the possible impacts of climate changes. This development provides a needed bridge between modelers and the users of the model simulations. One of the first major questions addressed by PCMDI is the issue of model resolution. Models used for climate studies have generally been run at resolutions dictated by available computer memory and time; researchers have undoubtedly paid a price for the limited resolution in previous studies of regional climate change. Initially, the resolution issue is being studied in the European Centre for Medium Range Weather Forecasts (ECMWF) operational model, which is recognized as the best in the world in weather forecasting. This model lends itself to resolution studies: it can be run at T-21, T-42, T-63, T-106, and T-213 (spanning 6 degree to 1/2 degree latitude grids). In an effort parallel to the resolution study, researchers plan to implement a preliminary diagnostics package with the ECMWF model to estimate the structure and distribution of systematic errors and their relation-ship to the model's parameterized physical processes. Particular attention is given to the diagnosis of the model's surface heat and hydrologic balance, its cloud-radiative forcing, and its portrayal of low frequency variability. Researchers are also developing a data bank for systematic model verification and a comprehensive model inventory. (RPIS 5135)

724. Cray Computer*W.L. Gates**(415) 422-7627*

\$2,000,000

To provide enhanced supercomputing to the climate modeling community, the National Energy Research Supercomputer Center at Lawrence Livermore National Laboratory has acquired an eight-processor Cray-2 computer. The computer was enhanced from 64 to 128 million words of memory, making it the most capable Class VI/VII supercomputer available to DOE and, in fact, to the U.S. Government. From this resource enhancement, the Carbon Dioxide Research Program is receiving an additional 3,000 computer resource units (CRUs), the equivalent of about 3,000 Cray-1 hours, in its base and "Grand Challenge" allocation. Supplemental resources to climate modeling projects are 12,000 CRUs. (RPIS 5351)

725. Carbon Dioxide Effects Research*M.C. MacCracken**K.E. Taylor**M. Perry**(510) 422-1826*

\$1,050,000

In Task 1, Climate Modeling and Data Analysis, of the project the overall purpose of this research is to sharpen estimates of future climate change that might occur as a result of energy-related activities. It focuses on the effects of the increasing atmospheric concentration of carbon dioxide. Primary objectives are (1) to determine the rate of climate change in response to prescribed radiative perturbations and (2) to increase understanding of the cloud feedback effects, which are uncertain but undoubtedly important in determining overall climate sensitivity.

In Task 2, Program Management, the objectives of this research are (1) to prepare technical reports and presentations providing state-of-the-art estimates of the climate effects of increasing CO₂ and the extent to which such changes have started to occur; (2) to help provide technical evaluation and coordination of the climate research component of the DOE CO₂ research program and to assist in integration of the research program; (3) to foster graduate and postdoctoral education through sponsorship of collaborative research within the university's system of campuses and laboratories; and (4) to sponsor special research to assist the DOE Carbon Dioxide Research Program enhanced model intercomparison studies.

Task 3, Global Climate Change Curriculum Development, is designed to provide elementary, middle, and high school teachers with the support necessary to develop effective, interdisciplinary instructional materials that address issues related to the problem of carbon dioxide build up in the Earth's atmosphere and the "greenhouse effect." By bringing together researchers of both scientific and nonscientific disciplines to focus on a problem of international concern, this program creates a setting in which the sciences are seen as relevant and beneficial to humanity. The program also inspires a valuable partnership between the scientific and educational communities. (RPIS 3028)

726. Computer Hardware Advanced, Mathematics, and Model Physics Initiative Organization*M.C. MacCracken**(415) 422-1826*

\$225,000

This project organizes the Computer Hardware, Advanced Mathematics, and Model Physics (CHAMMP) Program to accomplish the goal of developing a new generation of climate models able to provide convincing estimates of the potential time-dependent, regional changes in climate that may result from the increasing atmospheric concentrations of carbon dioxide and other greenhouse gases. The project will result in a report outlining the CHAMMP project's intent and implementation plan, suitable for review by the scientific community and coordination with other agency initiatives. The CHAMMP scientific program builds on a three-part strategy involving use of advanced computer hardware architectures, development and application of advanced mathematical approaches to representing the physics on massively parallel machines and analyzing and presenting the data, and use of improved representations of physical and chemical processes. Organizing this initiative involves a widely based collaborative effort feeding into a focused, mission-oriented objective. This involves outreach to and beyond both the climate modeling community and the few groups involved in climate modeling. Organizing this effort further requires a core scientific management team that works through contact and encouragement of other groups, workshops, and prototype studies. The organizational effort comprises three phases. In the initial phase, (which will last about 2 years), the community of researchers is assembled and involved in prototype studies that allow both study of the challenges to be faced and generation of versions of existing models that perform well in the massively parallel environment. Design criteria for the advanced climate model (ACM) are developed. In the second, or model development phase (covering about 4 years), an initial version of ACM is, through the close coordination of the efforts of many groups, actually constructed and tested on machines capable of increasing throughput by 10² to 10³. In the last phase, the model implementation phase (covering about 4 years), the initial ACM version is extended in its physics and transferred to even faster machines. Performance is further optimized, and useful model simulations are conducted. Throughout the project, close cooperation among a wide set of participants is needed. Ensuring this cooperative is, in addition to setting project objectives, the central task of the CHAMMP management activity. Workshops and communications are essential to fulfillment of this task. (RPIS 5377)

727. Trace Gas Interactions in the Global Atmosphere*D.J. Wuebbles**(415) 422-1845*

\$318,000

There are three major objectives for this project: (1) to understand the effects that increasing atmospheric concentrations of CO₂ and other trace gases may be having on global atmospheric chemistry and climate; (2) to understand the interactions

between climate, chemical, and radiative processes; and (3) to establish clear relationships between theoretical models and the measurements of atmospheric constituents being made in the troposphere and stratosphere. Major elements in these research studies are to (1) develop information on past trends and the potential for future trends of the various trace species, an effort being coordinated with studies of trace species histories and economic analyses being done at Pacific Northwest Laboratory; (2) examine budgets of relevant trace gases to better establish which uncertainties require consideration in the development of scenarios of future emissions; (3) extend existing capabilities for modeling global atmospheric chemical, radiative, and physical processes; (4) perform model sensitivity analyses to better define the mechanisms, key parameters, and overall uncertainties of potential trace gas influences on the atmosphere; and (5) establish a clearer relationship between theoretical models and the measurements of atmospheric constituents being made in the troposphere and stratosphere, with the purpose of defining and reducing existing uncertainties in the determination of trace gas effects. To accomplish this evaluation the Lawrence Livermore National Laboratory (LLNL) is extending present modeling capabilities and developing new models to allow coordinated treatment of chemical and climatic effects. The LLNL one-dimensional atmospheric chemistry-transport models have been reference models for past assessments. The LLNL two-dimensional model of tropospheric and stratospheric chemical, radiative, and dynamical processes is rapidly becoming the new standard for such assessments. Results of atmospheric chemistry perturbation studies with the two-dimensional model one being used to determine radiative perturbations, the climatic significance of which is evaluated with climate models. Efforts are also under way to develop a one-dimensional radiative-convective chemistry model and to couple the LLNL two-dimensional chemistry and climatic models for use in interactive simulations. (RPIS 4451)

728. Scientific Development of the Advanced Parallel Chemistry Climate Model

D.J. Wuebbles
(415) 422-1845

\$300,000

This project's objective is to lead the development of detailed simulation components of the chemical, radiative, and transport processes occurring in the global atmosphere during the development of the advanced climate model (ACM) under the Computer Hardware Advanced Mathematics, and Model Physics Program (CHAMMP). The project entails the following three tasks: (1) to determine the optimal treatment of the chemical and physical processes to be included in the model to ensure a high quality, but computationally efficient, product; (2) to design and develop the scientific components of the chemical, radiative, and transport submodels; and (3) to perform necessary studies to evaluate and validate the resulting submodels. (RPIS 5376)

Los Alamos National Laboratory

Los Alamos, NM 87545

Computing and Communications Division

729. Computer Hardware, Advanced Mathematics, and Model Physics

R.C. Malone
(505) 667-5925

\$735,000

In this project, the Los Alamos National Laboratory (LANL) provides technical leadership for the model development component of the DOE CHAMMP global modeling program. Laboratory personnel work with DOE management to (1) define the scope, objective, and timetable for CHAMMP; (2) help define tasks to be pursued under its auspices; and (3) identify well qualified personnel within DOE laboratories, universities, and other institutions to carry out those tasks. The researchers also fashion a well-integrated program that (1) complements the activities carried out under the proposal-driven Science Projects component and (2) establishes a technical framework that can incorporate advances made within the DOE High Performance Computing Initiative and the global climate modeling programs of other Federal agencies. (RPIS 5508)

730. Computer Hardware, Advanced Mathematics, and Model Physics CM-5 Support

A.B. White
(505) 667-4530

\$1,200,000

Access and resources are provided for CHAMMP investigators on the massively parallel CM-5 supercomputer at the Los Alamos High Performance Computing Research Center. CHAMMP investigators are allotted approximately 25 percent of CM-5 machine resources. (RPIS 5748)

Physics Division

731. Predictability in Numerical Modeling of Ocean Dynamics

L.G. Margolin
(505) 667-4843

\$170,000

The project objective is to apply nonlinear dynamical modeling methods to assess predictability and accuracy in computer models of the global ocean circulation. The project provides an analysis of the predictive potential found in ocean circulation models. Approximate Inertial Manifold methods are used to develop a subgrid scale parameterization for modeling ocean dynamics. The error estimate derived from the construction of the parameterization can be used to estimate the predictive skill of the full ocean model. (RPIS 5584)

Theoretical Division

732. Comparison of Methods for Solving the Spherical Shallow Water Equations on the Connection Machine

J.R. Baumgardner
(505) 667-9102

\$100,000

This project compares different formulations for solving the shallow water equations on a sphere. The project develops possible alternative approaches to existing formulations describing geophysical fluid dynamics in global climate models. A comparison of several different formulations of the shallow water equations on a rotating sphere is made for accuracy and efficiency on a massively parallel supercomputer. (RPIS 5586)

733. Massively Parallel Global Ocean Modeling

R.D. Smith
(505) 667-7744

\$200,000

The project develops a data-parallel version of the Semtner-Chervin eddy-resolving global ocean model for massively parallel supercomputers. An ocean circulation model for climate studies that runs efficiently on massively parallel supercomputers is the desired product. An existing state-of-the-science global ocean model was ported to the CM-2 massively parallel supercomputer as a prelude to installation on the CM-5 supercomputer, which is a factor of 100 more powerful. The model was restructured, and several algorithmic changes were made to increase its efficiency and capability. The model will be installed on the 2048 processor CM-5 as soon as the machine is available and diagnostic runs will be made. (RPIS 5587)

Oak Ridge National Laboratory Oak Ridge, TN 37831

Engineering Physics Division

734. Parallel Atmospheric Climate Model

R.C. Ward
(615) 524-6185

\$835,000

This project has several objectives: (1) to provide a usable parallel implementation of an existing model for use by modelers, (2) to investigate the coupling of the parallel atmospheric model with other components of a climate simulation system, (3) to produce algorithm libraries and software tools to aid in the development of parallel climate models, and (4) to sponsor workshops for sharing information among the climate modeling community.

First, parallel implementations of three existing methods in prototypes for multiple instruction, multiple data (MIMD) and single instruction, and multiple data (SIMD) machines are made. Both MIMD and SIMD parallel computers are being examined to maintain generality for the coupling of the

atmospheric model with other components of the global climate system. The aim of this work is to evaluate the suitability of these methods for large scale parallel execution. The prototypes apply the spectral method, finite difference method, and a composite mesh finite difference method to the nonlinear shallow water equations on the sphere. A portable parallel version of the National Center for Atmospheric Research's (NCAR) Community Climate Model Two, (CCM2), is being developed. This code is designed to run on distributed memory MIMD computers such as Intel iPSC/860, BBN Butterfly, and NCube machines. The Intel computer is the initial computational engine. The initial work modifies the existing CCM2 to (1) run on medium-grained parallel processors, (2) isolate sequential bottlenecks and other deficiencies in the existing algorithms, and (3) quantify load imbalances due to model physics. A portable version of the Cray code is being developed using profiling tools to identify computationally intensive components. A workshop is then held to discuss approaches to parallelization, and devise an initial strategy; the recommendations of the workshop are implemented incrementally using both Fortran and higher level languages. Both versions use PICL and other software tools for portability and performance evaluation and characterization. Regular workshops are held to integrate components developed at different institutions into the parallelized CCM2. Parallel algorithm development and enhanced physics can be smoothly incorporated within the same incremental framework. To address the computational problems associated with advanced model physics, the existing CCM2 is extended by coupling it with a vegetation model and the computational load of the coupled system is measured. The biosphere-atmosphere coupling uses the existing BATS interface to CCM2. The description of interaction between the atmospheric and terrestrial systems is restricted to exchange fluxes. Work on performance monitoring tools focuses on improving data reduction and collection techniques and on improving graphical tools for presenting decompositions and performance data. Existing tools are extended and validated for data reduction and collection on a parallel computer with approximately 100 nodes. Existing graphical tools are extended for visualizing the decompositions employed in the initial parallel version of CCM2 and the parallel algorithm prototypes. Finally, workshops are being held on tools and concepts of parallel programming for advanced climate models, numerical methods, and model physics. (RPIS 5379)

Math Science Division

735. Computational Support for Parallel Climate Modeling

R.F. Sincovec
(615) 574-3125

\$600,000

The computational requirements of the Computer Hardware, Advanced Mathematics, and Model Physics (CHAMMP) Program are supported by providing massively parallel computer resources and support for using these resources on the

Intel Paragon parallel supercomputers. This support enables the development of CHAMMP atmospheric, ocean, and coupled climate models. The High Performance Computing Research Center at Oak Ridge National Laboratory provides dedicated blocks of computer time to CHAMMP investigators. The Center staff assists CHAMMP researchers as the model codes are developed and exercised on the Intel Paragon. This activity results from the collaboration between the Office of Health and Environmental Research and DOE's Scientific Computing Staff to enhance progress on the Grand Challenge computing problem of numerical simulation of climate. (RPIS 5679)

Pacific Northwest Laboratory

Sequim, WA 98382

Battelle Marine Sciences Laboratory

736. Ocean Convection Parameterization

D.W. Denbo

(206) 683-3616

\$190,000

Parameterizations are developed for penetrative and nonpenetrative convection in ocean general circulation models (OGCMs). Convection parameterizations are incorporated into OGCM to increase the accuracy of deep water formation processes. This results in improved prediction accuracy for ocean-atmosphere coupled models. A set of parameterizations for mixed-layer dynamics, sea ice formation, and penetrative convective mixing is assembled and tested. The parameterizations are first tested in a one-dimensional model. These one-dimensional experiments determine the effectiveness of the schemes and help tune parameters such as the entrainment rates and convective time scales. Next, the parameterizations are incorporated into a modified version of the Byron-Cox OGCM. The OGCM experiments are performed in an idealized box domain representing the Greenland, Norwegian, and Iceland Seas. Idealized and observed surface forcing conditions are used, and the relative performance of the parameterizations in a model ocean basin is evaluated. (RPIS 5546)

Sandia National Laboratory

Albuquerque, NM 87185

Parallel Computations Science Department

737. Parallel Methods for Climate Modeling

J. Swishelm

(505) 845-7999

\$50,000

Fast algorithms are developed for the solution of geophysical fluid dynamics on massively parallel supercomputers. The project seeks improved performance of atmosphere and ocean general circulation models on massively parallel supercomputers. Expertise is applied in numerical methods to ocean and atmosphere computational modeling problems. (RPIS 5749)

Global Change: Climate Modeling and CHAMMP

Offsite Grants

Applied Research Corporation

College Station, TX 71840

738. Studies in Regional Climate Sensitivity, Predictability, and Temporal Response

T.J. Crowley

G.R. North

(409) 846-1403

\$150,000

The objectives of this project are to use noise-forced energy balanced models (nf-EBM) to study climate sensitivity to external forcing, regional climate response to increasing CO₂ concentration, the nonlinear effects of seasonal albedo changes, and differences in regional climate predictability resulting from geography. Preliminary estimates of climate sensitivities are being produced through multiple long-term integrations.

The research examines climate sensitivity using parameters from nf-EBM. The investigators contend that climate sensitivity can be determined from correlational functions computed from available climate data sets. An understanding of the relationships between climate sensitivity and parameters in nf-EBMs can be determined by comparing the correlations from the data with those from the model. Adjusting the parameters in the model to give correct correlations yields quantitative information about relationships among these parameters in the real climate system.

The timing of the regional climate response to increasing greenhouse gas concentrations may depend upon location. The variations result from the differences in thermal capacity between the land and oceans. Transport by the atmospheric and ocean general circulations is not explicitly included in nf-EBM, but it is accounted for by horizontal diffusion. The rate of diffusion is not sufficiently fast to overcome the land-ocean differences in the heat capacity, thereby producing geographically dependent lag in the timing of the climate systems response to greenhouse warming. Coupling nf-EBM with an ocean upwelling diffusion model currently simulates the ocean's role in delating potential climate warming.

The investigators are separating the linear and nonlinear effects of nf-EBM runs by performing a statistical comparison of a version with an interactive snow albedo coupled to a seasonal cycle to a version without interactive albedo. They are also exploring the use of the nonlinear nf-EBM in the two studies.

The investigators have developed more sophisticated statistical methods to determine the capacity of several nf-EBMs to perform decade to century climate predictions. These methods provide useful techniques for subsequent analysis of long general circulation model runs. (RPIS 10558)

University of Arizona

Tucson, AZ 85721

Institute of Atmospheric Physics

739. The Land Component of the Global Climate System with Adequate Spatial Resolution

R.E. Dickinson

(602) 621-2810

\$123,000

The objective of this project is to develop land surface process parameterizations for general circulation models (GCMs). The product of this research fills a large technical gap in current climate model approaches to describing land surface. An improved biospheric-atmosphere transfer scheme (BATS) parameterization is potentially a valuable resource to the Computer Hardware, Advanced Mathematics, and Model Physics program.

Research objectives are being accomplished through the following tasks:

(1) Recoding, restructuring, and documenting the current BATS code to make it conform to programming standards now adopted by the climate modeling community. Subsequently, experiments are performed to identify shortcomings and weaknesses for the next stage of development.

(2) Developing a version of this code to conduct simulations at 0.5 degree land surface resolution that is independent of GCM grid solution.

(3) Developing a subgrid scale description from GCM grid scale average precipitation, radiation, and cloudiness for use in the BATS parameterization.

(4) Conducting sensitivity experiments with BATS implemented within the National Center for Atmospheric Research's Community Climate Model (Version 2), a state-of-the-science spectral transform climate model, to test the scheme's ability to simulate climate anomalies.

(5) Developing simple visualization tools to enhance evaluation of fine-mesh output. (RPIS 10544)

Brown University

Providence, RI 02912

Department of Geological Sciences

740. Sensitivity of Climate Models: Comparison of Simulated and Observed Patterns for Past Climates

W.L. Prell

T. Webb III

R.J. Oglesby

(401) 863-3221

\$425,000

The project's objective is to validate the National Center for Atmospheric Research general circulation model (NCAR GCM) against paleoclimatic data.

The GCM is being validated against past climate, current climate, and the detailed time series of the instrumented record for the last 150 years to complete a comparison between paleoclimatic data and NCAR GCM.

The research focuses on (1) using general circulation models to simulate a series of climatic changes from the past, (2) providing assembled paleoclimatic data from large areas of the tropics and the northern hemisphere mid-to-high latitudes for the comparison of model simulations and observations, (3) developing methods and procedures for improving the comparability of the observed and simulated data, and (4) comparing the model results with the paleoclimatic data. The Cooperative Holocene Mapping Project book is being completed. (RPIS 9342)

University of California, Los Angeles

Los Angeles, CA 90024

Department of Atmospheric Sciences

741. Development of an Advanced Finite-Difference Atmospheric General Circulation Model

A. Arakawa

C.R. Mechoso

(213) 825-1852

\$140,000

The objective of this research is to develop a higher resolution finite-difference model with improved process parameterizations (i.e., the way the model describes physical processes like cloud development, atmospheric radiative transfer, surface energy exchange, etc.) suitable for a massively parallel computing environment.

The investigators are providing the Computer Hardware, Advanced Mathematics, and Model Physics (CHAMMP) Program with a documented copy of the current model code and working with CHAMMP researchers to install the code on a parallel supercomputer. The intention is to make the model available to CHAMMP science team investigators for their research. As improvements to the model are made at CSU and the University of California at Los Angeles, they are transferred to the CHAMMP community.

The investigators are developing improved physical parameterizations for cloud processes, convection, land surface exchange, and the planetary boundary layer. This task is essential because these parameterizations are based upon information from recent observational programs and theoretical advances. These efforts are partially supported by other funding agencies, particularly NASA.

The investigators are also improving the computational framework of the model. Recent developments in more accurate numerical methods are being incorporated into the model so that it more faithfully simulates the real atmosphere. These improved formulations partially overcome the inaccuracies in finite-difference modeling that gave rise to the spectral models. Of particular importance is the improved representation of flow near the poles, which has been problematic in global finite-difference models utilizing a spherical coordinate system.

The investigators are running sensitivity experiments to test the improved parameterizations and methods as a function of model resolution. It is well known that models perform better at higher resolution because the process parameterizations are more faithful to the real world at finer spatial scales. These sensitivity tests examine how well the parameterizations scale with different grid spacings. (RPIS 10549)

University of California, San Diego
La Jolla, CA 92093

Institute for Nonlinear Science

742. Symmetric Truncation of the Shallow Water Equations

S. Rouhi

(619) 534-1675

\$112,000

The objective of this research is to develop a novel framework to model geophysical fluid dynamics that may be superior to currently used methods. The alternative numerical methods being developed for general circulation models (GCMs) of the atmosphere and ocean can be executed easily on massively parallel computer systems.

It is postulated that the inviscid Lagrangian formulation of the shallow water equations belongs to a mathematical class of systems known as Hamiltonian, or friction-free, systems. In such a system, infinitely many conservation properties exist theoretically, many of which may be relevant to the global geophysical flow problem. Symmetric truncation is being used to develop a model system in which the number of conserved properties increases as the degrees of freedom in the model increase. This system is used to explore the relationship between conserved properties and accuracy of the model.

As a next step, the investigator uses a method called "reduction" to cast the model in the Eulerian framework that is ultimately required in a full climate model. The systematic examination of accuracy and conservation that is performed first defines how the Eulerian model must be constructed. Finally, the investigator extends the shallow water model to continuously stratified flow, which is a much more realistic approach for characterizing the atmosphere and ocean. (RPIS 10546)

University of Colorado
Boulder, CO 80309

Institute of Arctic and Alpine Research

743. Studies of Water Infiltration and Runoff in Subfreezing Snow on Regional Scales to Estimate Future Greenhouse-Induced Changes in Sea Level

M.F. Meier

T.H. Illangasekare

(303) 492-7909

\$169,000

The objective of this research is to forecast future sea level change due to greenhouse-induced changes in runoff from polar glaciers and ice caps. The eventual product of this research will be a model to predict the development of impermeable firn (and consequent runoff and discharge to the ocean) in response to predicted future climate change. Project researchers (1) observe in the field the processes of infiltration and refreezing that lead to the formation of impermeable firn layers, (2) reproduce these observed processes in the laboratory and confirm and further quantify understanding, (3) develop and calibrate a regional scale numerical model that can simulate these processes based on measured parameters and driven by boundary conditions determined by climate, and (4) apply this model to predict the development of impermeable firn (and consequent runoff and discharge to the ocean) in response to predicted future climate change. (RPIS 10372)

Colorado State University
Fort Collins, CO 80532

Department of Atmospheric Sciences

744. Parameterizations in High Resolution Isopycnal Wind-Driven Ocean Models

T. Jensen

D.A. Randall

(303) 491-8533

\$57,000

The research develops a high resolution isopycnal-coordinate ocean circulation model that can be used to test the usefulness of the isopycnal modeling approach for climate prediction. Isopycnal ocean model formulations use spherical coordinates to describe the two horizontal dimensions that are parallel to the Earth's surface and constant potential density surfaces or isopycnics as the vertical coordinate. In the absence of diabatic effects and mixing, ocean fluid parcels traverse along isopycnal surfaces. This property has advantages in finite-difference numerical forms of the equations of motion, because artificial numerical mixing is reduced as the equations are integrated. Because isopycnal surfaces are not fixed in space, other problems associated with this coordinate system can arise to offset its advantages. These issues are explored to determine if isopycnal coordinate models are preferable alternatives to the models employing the standard vertical coordinate in global ocean modeling. (RPIS 10531)

745. The Role of Clouds in Carbon Dioxide-Induced Climate Change*D.A. Randall*

(303) 491-8474

\$190,000

The project objective is to (1) develop a quantitative understanding of surface radiative forcings as related to clouds and cloud climate feedbacks on climate change and (2) develop an advanced ocean/atmospheric general circulation model (GCM). The expected products are (1) an understanding of the surface radiative forcings, relative to the clouds, from the various GCMs, how the models compare with the available observations, and possible methodological shortcomings and (2) an improved GCM with fully coupled ocean and atmosphere. The research focuses on the radiative role of clouds in current climate and in a climate modified by increased atmospheric concentrations of CO₂.

Specifically, the research addresses the role of clouds through five related research tasks. The connecting theme is to identify the differences among the GCMs and provide for improved physical parameterization of clouds in the GCMs. Under task 1, 14 GCMs will be compared by looking at surface fluxes (sensible, latent heat, infrared, and solar), precipitable water content, and precipitation and evaporation. This work is being done in cooperation with Lawrence Livermore National Laboratory and State University of New York at Stony Brook led GCM intercomparison. In task 2, differing cloudiness parameterizations are being studied in a simple coupled ocean/atmosphere model as atmospheric CO₂ concentrations change. This task provides a simple educational tool to guide and assist in understanding the effect of these modifications to the cloudiness schemes when used in the GCMs. The former runs on desktop computers while the latter can require 10 to 100 hours on a supercomputer. Task 3 integrates the observational research programs, the GCM development, and intercomparison research proposed for the Carbon Dioxide Research Program. Cloud data from satellite, aircraft, and balloons are used to quantify cloud forcing and feedback processes as observed. Tasks 4 and 5 provide a step-by-step process for adding an ocean GCM to the existing Colorado State University (CSU) atmospheric GCM. The mechanics are simple; however, coupled GCMs magnify the imperfections of the models being brought together. Understanding the physical and methodological problems and then making appropriate, physically-based corrections is difficult. The primary concern is the effect on clouds. For example, simple changes in ocean albedo can have a dramatic impact on model cloudiness requiring modification of the cloud parameterizations. Task 4 develops the Q-flux version of the ocean model. Task 5 takes the final step and couples the CSU GCM with an ocean GCM. (RPIS 0121)

746. Development of an Advanced Finite-Difference Atmospheric General Circulation Model*D.A. Randall*

(303) 491-8474

\$89,000

The objective of this research is to develop a higher resolution finite-difference model with improved process parameterizations (i.e., the way the model describes physical processes like cloud development, atmospheric radiative transfer, surface energy exchange, etc.) suitable for a massively parallel computing environment to carry out climate prediction studies.

The investigators are providing to the Computer Hardware, Advanced Mathematics, and Model Physics (CHAMMP) Program a documented copy of the current model code. They are working with CHAMMP researchers to install the code on a parallel supercomputer, with the intent of making the model available to the CHAMMP science team investigators for their research. As improvements to the model are made at Colorado State University and the University of California at Los Angeles, they are transferred to the CHAMMP community.

The investigators are developing improved physical parameterizations for cloud processes, convection, land surface exchange, and the planetary boundary layer. These efforts are partially supported by other funding agencies, particularly the National Aeronautics and Space Administration. This task is essential because these parameterizations are based upon information from recent observational programs and theoretical advances.

The investigators are improving the computational framework of the model. Recent developments in more accurate numerical methods are being incorporated into the model so that it more faithfully simulates the real atmosphere. These improved formulations partially overcome the inaccuracies in finite-difference modeling that gave rise to the spectral models. Of particular importance is the improved representation of flow near the poles, which has been problematic in global finite-difference models utilizing a spherical coordinate system.

The investigators are running sensitivity experiments to test the improved parameterizations and methods as a function of model resolution. It is well known that models perform better at higher resolution because the process parameterizations are more faithful to the real world at finer spatial scales. These sensitivity tests examine how well the parameterizations scale with different grid spacings. (RPIS 10561)

Columbia University

New York, NY 10025

Center for the Study of Global Habitability**747. The Impact of Recent Model Improvements on
Goddard Institute for Space Studies General
Circulation Model Predictions of Climate Change***L.M. Druyan*

(212) 678-5564

\$52,000

Three new parameterizations are tested and incorporated into the NASA Goddard Institute for Space Studies (GISS) general circulation model (GCM). This significantly advances the GISS GCM version being used in the DOE climate model intercomparison and diagnosis program. The focus of the program is to understand the physical and methodological mechanisms responsible for the agreements and disagreements among climate model calculations. This provides a basis for model improvement. Three new parameterizations being developed and tested for the GISS GCM: (1) moist convection, (2) ground hydrology, and (3) planetary boundary layer (PBL).

Moist convection is a new parameterization that seeks to parameterize the down drafts at convective-scale to prevent the model tendency to be too dry. Upper humidity and temperature profiles are improved by using a two-part convective scheme for entraining and nonentraining convective plumes.

The ground hydrology parameterization includes multiple soil layers, hydraulic conductivity, soil texture, surface and subsurface transport, and evapotranspiration. The PBL parameterization is improved by incorporating eddy transfer coefficients that better match observations. Improvements occurred in convective precipitation and surface wind and temperature calculations.

Each calculation is tested separately and together at three model horizontal resolutions of $8^\circ \times 10^\circ$, $4^\circ \times 5^\circ$, and $2^\circ \times 2.5^\circ$. The $8^\circ \times 10^\circ$ resolution is being used to tie back to the original model formulation. Tests are run with the boundary conditions for the 10-year Atmospheric Model Intercomparison Program, as appropriate. (RPIS 10732)

Columbia University

Palisades, NY 10964

Lamont-Dohterty Geological Observatory**748. Recent Changes of Weather Patterns in North
America***G. Kukla**T. Karl*

(914) 359-2900

\$218,000

Researchers have two main objectives for this project: (1) to develop the data sets to evaluate changes in the properties and frequencies of air masses and extreme weather events over North America, including the variability of these properties,

and (2) to compare any observed changes to climate model predictions of greenhouse gas and aerosol-induced climate change.

Surface and upper air databases from the National Climatic Data Center and from other ongoing DOE research are being used to develop the air mass and extreme event data sets. As the study progresses, data from China and the U.S.S.R. (also under development by DOE) are used to extend the results to the Northern Hemisphere.

The approach includes four steps:

(1) The air mass types are defined primarily in the areas of humidity and free atmosphere wind direction. Each type is characterized and analyzed in terms of weather events, temperature, cloud fraction, etc.

(2) The frequency of air mass type changes is analyzed for relationships to warm/cold years and El Niño/La Niña years.

(3) The variability and changes (e.g., any trends) within air mass type are documented. The temperature and precipitation extremes within an air mass are analyzed along with the time-related changes.

(4) The results of the analyses produced during the first three steps are compared with climate calculations.

The research addresses the following sets of questions:

(1) Are there any systematic time-related changes in the air mass frequencies in North America? If so, how do they compare with model calculations? The answers to these questions assist researchers in model development, as well as in assessing cause and effect.

(2) Are there any systematic time-related changes in the temperature of comparable air mass types? If so, how do they compare with model calculations?

(3) Are there any changes in the precipitation patterns (over North America), and do they relate to the changing frequency patterns, persistence, or character of the air mass types? (RPIS 9436)

University of East Anglia

Norwich NR47TJ, United Kingdom

School of Environmental Sciences**749. Detection of CO₂-Induced Climate Change***T.M.L. Wigley**P.D. Jones*

011-44-603-56161

\$168,000

In addition to variations in greenhouse gas concentrations, climate responds to a number of other forcing factors—changes in ocean circulation, volcanic activity, solar irradiance, etc. To detect the greenhouse effect, its signal must be isolated from the "noise" of natural climatic variability, a significant part of which is due to these other factors. A high quality, spatially extensive database is required to define the noise and its spatial characteristics. To this end, this project assembles and analyzes instrumental climate data and develops simple climate models as a basis for (1) detecting greenhouse gas-induced

climatic change and (2) validating general circulation models (GCMs). Available land and marine databases are updated and expanded, and differences between different data sets are reconciled where possible. The data are analyzed to determine the potential effects on climate of greenhouse gas concentration changes and other factors. Analyses are guided by simple energy balance climate models. These analyses are oriented towards obtaining early evidence of greenhouse gas-induced climatic change that would lead to confirmation, rejection, or modification of model projections and toward the statistical validation of GCM control runs. The data analyses focus on the use and development of appropriate statistical techniques for signal detection and pattern recognition. Interpretations are guided by specially developed energy balance climate models. Fully documented computer programs are produced for (1) a hemisphere-hemisphere and land-ocean resolving energy balance climate model and (2) statistical significance testing of differences in means, variances, and spatial patterns using test statistics specifically designed for the validation of GCMs. A gridded, homogenized sea surface temperature data set is being produced for the period prior to 1900. Estimates of global-mean surface air temperature based on both land and marine data are made continuously on a monthly basis. (RPIS 9464)

University of Illinois
Urbana, IL 61801

Department of Atmospheric Sciences

750. Greenhouse Gas-Induced Climate Change

M.E. Schlesinger
(217) 333-2192

\$130,000

The primary objectives of this research are (1) to analyze the feedbacks in the CO₂-induced warmings simulated by the two-level model and the new multilevel model, (2) to analyze the causes of the CO₂-induced drying in the Northern Hemisphere continents in the summer as simulated by the models, (3) to analyze the CO₂-induced changes in the diurnal cycle simulated by the multilevel model, and (4) to analyze the cloud optical feedbacks on CO₂-induced climate change. To accomplish these objectives, the research includes two areas. The first concentrates on the first three objectives to understand the equilibrium and transient climate change and the second concentrates on the cloud optical feedback (objective four). Multitasked versions of the general circulation model (GCM) will be developed as part of the overall approach. One task concerns equilibrium and transient climate change. The research addresses two questions: (1) Why does the CO₂-induced warming in the model increase as the temperature of the control (1 x CO₂) decreases? and (2) Is it the effect of ice-albedo feedback, cloud-cover feedback, or a combination of these and other feedbacks? To answer these questions, the research quantitatively determines the range of model feedbacks as part of the overall DOE program of model diagnostics. A radiative-transfer model previously developed is used. The research next

addresses the following question: What model mechanism is responsible for the summer, midcontinental drying in this GCM? The soil water balance in the model is quantitatively analyzed to determine the model mechanism. This lays the basis for improvements in the soil water modeling subcomponent of GCM. To develop a basis for the detection of climate change, researchers are comparing the model's diurnal cycle of temperature to the 1 x CO₂ and the 2 x CO₂ experiments. Observations analyzed in other DOE research suggest that the diurnal range of temperature should decrease. The daily maximum is dominated by solar heating, so the CO₂ should have little impact while the nighttime low may show a large impact of CO₂-warming, i.e., getting warmer, so the range decreases. Testing the model for this possible phenomena provides a possible piece of a specific CO₂ fingerprint. A transient model run is conducted to provide a basis for the comparison with the observation over the past 100 years. To carry out this experiment, it is necessary to verify the new ocean GCM. This is done by comparing the observed ocean tracer data (e.g., the penetration of bomb tritium) with the model estimates of the trace distribution. Subsequently, the coupled model will be run with 1 x CO₂, 2 x CO₂, and in a transient mode with slowly increasing greenhouse gases. The results are intercompared as well as compared to the observed record of climate. As the basic strategy to detect climate change, multiple variables are examined—"the fingerprint theory of climate change detection." Another task concerns cloud optical feedback. Recent GCM research has shown that the model sensitivity can change by a factor of 2 when cloud optical properties are changed or calculated rather than prescribed. Research continues to develop more physically based parameterizations for incorporation in the GCM, including a new boundary layer parameterization. This research is supported in collaboration with the National Science Foundation. (RPIS 10283)

Iowa State University
Ames, IA 50011

Department of Geological and Atmospheric Sciences

751. Modeling of Land-Surface/Atmospheric Dynamics for CHAMMP

W.J. Gutowski
(515) 294-5632

\$170,000

The land surface hydrological and vegetative effects are accurately described in general circulation models (GCM). The project's model parameterization incorporates land surface processes and feedbacks with the atmosphere. An existing model of land surface-atmosphere exchange and surface hydrology is extended and uses a single column version of an atmospheric GCM as the development testbed. (RPIS 10712)

University of Maryland
College Park, MD 20742

Cooperative Institute for Climate Studies

752. Exploitation of Parallelism in Climate Models

F. Baer

(301) 405-5387

\$273,000

The objective of this research is to explore new methods of general circulation model (GCM) structure and execution that exploit massively parallel computer systems. Products of this research include improved methods for describing physical processes in atmospheric and ocean GCMs, the development of new algorithms to execute these models on massively parallel computer systems, and the use of the models for climate prediction studies.

Current GCMs require all grid points on the model to be marched forward concurrently, a step requiring communication and synchronization between the parallel processors. The investigators are exploring new algorithms that allow the concurrent computation of several time levels in a GCM. These "time compression" algorithms require that the models be restructured so that the communication is minimized.

The investigators are developing local subgrid scale models that provide the time and space averaged statistics to a climate model. These subgrid models have a resolution that is independent of that of the climate model so as to encompass the appropriate range of spatial and temporal scales needed to simulate the physical processes.

The investigators are utilizing massively parallel architectures to concurrently execute multiple model simulations to form an ensemble set of climate realizations. The simulation employ different initial conditions so as to generate enough realization to constitute an ensemble climate. (RPIS 10579)

Department of Meteorology

753. Variability and Predictability of the Coupled Ocean-Atmosphere-Land Climate System

J.L. Kinter

(301) 405-5384

\$100,000

The research quantifies model uncertainties and internal climate model variability that result from general circulation models (GCM) predictions and analyzes the systematic errors and climate statistics generated by long GCM runs. An existing state-of-the-science GCM performs variability and uncertainty studies. Quantification of the internal atmospheric variability is made by comparing long runs of a high resolution atmospheric GCM using a specified annual cycle of sea-surface temperature to long runs with the atmospheric model coupled to a dynamic ocean. There is a possibility that the statistics of the short-term variability are different between the two sets of simulations. Multiple atmospheric model simulations are conducted to examine the sensitivity of the predicted climate to resolution. (RPIS 10530)

754. Volcanic Signal in Global Change

A. Robock

(301) 405-5089

\$50,000

The objectives of this research are (1) to develop an improved volcanic index for climate analysis and (2) to analyze the observed climate record (surface temperature) for evidence of volcanic-induced cooling—including comparison with general circulation model (GCM) calculations. The research is divided into three areas: (1) volcanic index development, (2) comparison of the index to the climate observations, and (3) GCM calculations and comparison to the data. Questions addressed are (1) Is there a preferential time of year and/or latitude of a climate response? (2) Do the land and ocean data both show a signal, and how do they compare? (3) On the timescale months, is there a strong signal? and (4) Could the El Chichon eruption have contributed to the strength of the 1982-1983 El Niño? A wide range of volcanic indices have been developed. The range includes the well-known Lamb dust veil index (DVI) based on historical reports, temperatures, optical phenomena, and some solar radiation measurements as well as geological indices based on the explosivity of the volcano (VEI). DVI is primarily an annual hemispheric average index; using DVI makes it (1) difficult to determine regional and seasonal effects or (2) to drive a GCM. This research develops a new index based on a variety of quantitative measures and examines the existing volcanic indices to establish a time series for use with climate models (ideally, an estimate of atmospheric aerosol concentrations). Data analysis addresses the first three questions posed above. The research analyzes the surface temperature record over the last 150 years and compares it to the newly developed volcanic index. The resulting information should provide a clearer understanding of the relationship between natural variability of the climate cause-and-effect mechanisms such as volcanic activity. This will contribute to the DOE effort to quantitatively link CO₂ and other trace gas increases to climate change by reducing unexplained noise. The GCM analysis further assesses cause and effect. The analysis is initiated when appropriate. This work is supported in concert with the National Science Foundation. (RPIS 10284)

University of Massachusetts
Amherst, MA 01003

Department of Geology and Geography

755. Climate System Research: Studies of Global and Regional Instrument Data

R.S. Bradley

(413) 545-2794

\$169,000

This project's objectives are to (1) extend the DOE long-term surface climate data set for regional analysis, (2) analyze the data for critical regions with special climate characteristics likely to change under CO₂-induced climate change, (3) assess spatial and temporal coherence of hydrological variability, and

(4) compare the regional data to climate modeling results. The basic climate data set (prepared under past and continuing grants to the University of East Anglia) is improved by assessing the quality of additional temperature and precipitation measurements from the U.S.S.R. These data have been obtained under the U.S.-U.S.S.R. bilateral agreement and now require examination and incorporation into the data set. The Soviet data set is important because the territory it covers is large; thus, the data may significantly influence Northern Hemispheric averages (e.g., surface air temperatures). The significance of the additional data is being evaluated and used to test for regional urban warming. Models and paleoclimate analyses suggest that high latitude and high altitude environments and arid and semiarid marginal zones will be sensitive to climate change. To establish the climate in these regions as a basis for assessing change and for testing climate models, special regional data bases are developed. These data include sea ice, surface and low level atmospheric temperatures, and precipitation. The research attempts to evaluate the evidence for climate change in these regions relative to global changes. Climate models predict changes in precipitation (a global increase with regional increases and decreases) and increased temperatures. Any changes in the amount and type of rain or snow combined with temperature changes can affect stream flow and other hydrological variables. The existing data sets are evaluated and compiled for assessing changes and for testing climate models. The above data sets and subsequent analyses are compared to climate model results. The research's end product is an updated global set of station and 5x10 gridded temperature and precipitation coverage data. The data set will be analyzed for patterns of regional and hemispheric climatic change for comparison with general circulation model projections of greenhouse gas-induced climatic change. (RPIS 9942)

Massachusetts Institute of Technology Cambridge, MA 02139

Center for Meteorology and Physical Oceanography

756. Development of an Advanced Representation of Cumulus Convection

K.A. Emanuel
(617) 253-2462

\$91,000

The simulation of climate with general circulation models (GCMs) requires the accurate description of cloud effects. Cumulus clouds are active in the vertical mixing of atmospheric water, heat, and momentum. The objective of this research is to develop a new model of cumulus transport within GCM. This model uses a different hypothesis from the entraining cloud model now in widespread use. The new model instead adopts an episodic mixing approach, in which parcels enter the cloud at cloud base, move vertically through the cloud in updrafts without mixing, then instantaneously mix with their environment upon reaching the neutral buoyancy level. Cloud micro-physical parameters determine the amount of cloud

water converted to precipitation. This method may be more appropriate than the current schemes are for describing cumulus transport. (RPIS 10551)

National Academy of Sciences Washington, DC 20418

757. Polar Research Board

S. Abbott
(202) 334-3487

\$40,000

The Polar Research Board is a multidisciplinary body represented by members in marine and terrestrial biology, earth sciences, engineering, medicine, physical sciences, and social sciences. Members are drawn from academic institutions, industry, and national laboratories. In addition, the Board always has one member representing Canadian research activities. Federal agencies such as DOE, with programs in the Arctic or the Antarctic, have liaison representation on the Board and brief the Board periodically at its meetings on these activities. The project objectives are (1) to advise on U.S. and international policies and research of the Arctic and Antarctic, (2) to represent the U.S. within the Scientific Committee on Antarctic Research (SCAR), and (3) to plan for future polar research studies. The project (1) maintains awareness of research programs in the polar regions and advises Federal agencies on their polar programs when requested; (2) serves, on behalf of the National Academy of Sciences and the U.S. scientific and engineering community, as the U.S. National Committee for SCAR of the International Council of Scientific Unions, and as the U.S. Committee for the International Arctic Science Committee; (3) organizes and conducts studies that assess research needs in the various disciplines of polar science and offers recommendations on promising directions for future research, research priorities, and the facilities, data management, and logistics support required to achieve these research goals; and (4) provides a semiannual forum for the exchange of information about Federal agency activities in both polar regions and the research plans and programs of national and international organizations concerned with polar science and engineering research. This project also encourages U.S. awareness of and cooperation in international research and data-sharing activities in the polar regions, and maintains awareness of and assists with other activities of the National Research Council that relate to the polar regions. Information from the Board's activities will be useful to the Climate Systems and Resource Analysis programs. (RPIS 10215)

758. Board on Atmospheric Sciences and Climate

J.S. Perry
(202) 334-3517

\$50,000

The objective of this project is to provide scientific leadership and guidance to the Federal Government on important national and international issues in the atmospheric sciences and climate. The project supports regularly scheduled board, committee, and panel meetings that review current national and

international issues and provide advice and assistance to the Federal Government as needed. The Board on Atmospheric Sciences and Climate (BASC) has four major tasks: (1) to provide scientific leadership and guidance to the Federal Government on important national and international issues in the atmospheric sciences and climate and on the coordination between discipline-oriented activities within the atmospheric sciences and interdisciplinary programs such as the International Geosphere-Biosphere Program (IGBP); (2) to continue the activities of the Climate Research Committee (CRC) and, under the CRC, the Tropical Ocean-Global Atmosphere (TOGA) and International Satellite Cloud Climatology Project (ISCCP) Advisory Panels in providing guidance on U.S. participation in the World Climate Research Program (WCRP) and on TOGA, ISCCP, World Ocean Circulation Experiment, and other WCRP activities and on related national climate research activities; (3) to continue the activities of the Committee on Atmospheric Chemistry (CAC) as it continues to focus its efforts on issues raised by contemporary atmospheric changes, such as increases in greenhouse gases, stratospheric ozone depletion, and acid deposition; and (4) to maintain a capability to respond rapidly and effectively to requests by Federal agencies and Congress for evaluations, guidance, recommendations, and support in the areas of atmospheric science and climate. (RPIS 10462)

National Center for Atmospheric Research Boulder, CO 80307

Climate and Global Dynamics Division

759. Scientific Development of a Massively Parallel Ocean Climate Model

R.M. Chervin
(303) 497-1339

\$98,000

The objective of this research is to develop a resolving ocean general circulation model (OGCM) to run on massively parallel scientific supercomputers. Research is being conducted on (1) heat transport by ocean circulation, (2) the effects of near-surface processes and their model parameterizations on long-term climate simulations, and (3) model resolution requirements for climate modeling studies of ocean circulation. (RPIS 10564)

760. Improvement in Moist and Radiative Processes in Highly Parallel Atmospheric General Circulation Models: Validation and Development Through the CHAMMP Program

J.J. Hack
(303) 497-1387

\$164,000

State-of-the-science process parameterizations are developed for use in atmospheric general circulation models (GCMs) running on massively parallel computer architectures. The three products include (1) development of a model testbed to provide a convenient and efficient development environment to test the

parameterizations, (2) moist convective process representations with proper scale selection for atmospheric GCMs, and (3) atmospheric radiative transfer representations for GCMs. As climate model resolution increases, the process representations for convection and radiative transfer must properly scale with the spatial grid sizes of the model. Additionally, one of the principal weaknesses with current GCM-based climate models is their inability to properly treat clouds and radiative transfer with enough accuracy to reduce the large uncertainty found in recent simulations of greenhouse-gas-induced climate change. The investigators intend to improve the parameterizations for these processes with information available from recent field data and detailed model results. To provide a framework for rapid and efficient testing of these parameterizations, the investigators will build one- and two-dimensional reduced versions of GCMs that will simulate the performance of the parameterizations within a GCM context. This work lies at the intersection of CHAMMP with the Atmospheric Radiation Measurement program and provides a foundation for the convergence of the programs in the future. (RPIS 10535)

761. Enhanced Research Program on the Long-Range Climatic Effects of Increasing Atmospheric Carbon Dioxide

W.M. Washington
G. Meehl
(303) 497-1321

\$392,000

The primary objectives of this research are to (1) couple the advanced atmospheric CCMO and the advanced $1^\circ \times 1^\circ$ dynamical ocean general circulation model (GCM) and (2) perform a series of sensitivity experiments with the coupled and uncoupled models, including transient CO_2 experiments. The product of this research will be an advanced GCM capable of regional climate calculations. The research includes two tasks. Task 1 performs a control run ($1 \times \text{CO}_2$), an instantaneous $2 \times \text{CO}_2$ experiment, and a transient experiment. These experiments are done with the new atmospheric GCM. This set of experiments is necessary to compare the new version of the model against the previous results and therefore provide a basis for analyzing the experiments conducted with the advanced dynamical ocean, i.e., to understand the differences and assess the improvements. Task 2 couples the two advanced models. The dynamical ocean model is a $1^\circ \times 1^\circ$ version of the Semtner-Chervin $1/2^\circ \times 1/2^\circ$ ocean model with 20 vertical levels. The $1^\circ \times 1^\circ$ version of the Semtner-Chervin used in this research does not explicitly resolve the mesoscale eddies as does the parent model, but research has shown that observed ocean features sufficient for climate experiments can be simulated without such an explicit calculation. The research with the coupled model tests this hypothesis. The coupling scheme is synchronous rather than the often used asynchronous coupling. Asynchronous coupling does not allow for the time evolution of the interaction between the ocean and atmosphere. In the National Center for Atmospheric Research scheme, the atmospheric model provides wind stress, precipitation minus evaporation, and the sum of the surface energy balance to the ocean. The ocean provides surface temperature and sea ice information to the atmosphere. The

coupled experiment starts from separate runs of the new models, each "forced" with the appropriate observed climate conditions, e.g., the observed sea surface temperature for the spinup of the atmospheric model. This allows separate diagnosis of any model problems before coupling. The result will be the first coupled GCM experiments with an ocean model sufficient to simulate primary ocean climatological features. (RPIS 10265)

National Climatic Data Center

Asheville, NC 28801

762. Data Preparation and Analysis for Annex III, U.S./ People's Republic of China Cooperation in the Field of Atmospheric Trace Gases

T.R. Karl

(704) 259-0319

\$244,000

The objectives of this research are (1) to develop comprehensive regional climate reference data sets and (2) to quantify and understand regional climate change in the U.S. and China by using both observations and general circulation model (GCM) calculations (model control climates). Changes in any single climate element must be understood in context with changes in the rest of the components of the climate system, especially when examining regional sets. For example, a shift in the normal storm track could be the cause of a regional temperature change that enhances or modifies any CO₂-induced temperature increase. Annual and seasonal statistics of a specific element are insufficient for detection strategies. Compilation of comprehensive data sets (on a regional basis) is required. The research requires information on surface quantities such as precipitation, moisture, temperature, snow cover, etc., as well as information on clouds, temperature, moisture, pressure, and wind above the surface. Seven subtasks are required so that the National Climatic Data Center can provide regional data sets for the contiguous U.S. and Alaska. Alaskan data are included because the GCMs predict large and early changes in the polar regions. These subtasks involve collecting the manuscript data, keypunching the data, providing quality control for the data from station histories, and merging the data with existing databases. Climate statistics are being derived from the regional climate reference data sets and analyzed in context with GCM equilibrium and perturbed experiments.

The research is organized into eight subtasks. The first two subtasks of this task develop the Climatological Prediction by Model Statistics (CPMS) and test the model results against the observations. After developing and testing the CPMS, the second subtask examines the changes in the CPMS as CO₂ is increased in the model. If successful, the technique will provide a methodology for estimating regional climate change from the GCM results. Three of the remaining subtasks compare model fields to observations including the diurnal temperature range, upper atmospheric variables (e.g., temperature and pressure height), and multidimensional analysis of surface and upper air variables. Subtask 5 attempts to quantify

any urban heat island in China, key to determining the cause of global warming. Subtasks 7 and 8 analyze new and expanded data sets. Subtask 7 studies concomitant changes in snow depth and temperature to determine any long-term evidence for early spring snow-melt. Subtask 8 examines the improved Alaskan data set for changes. The U.S. urban heat island is often used to estimate urban effects on the global data set; its scientific basis is not established. This research will be one of several worldwide efforts to document differences in urban heat island effects. (RPIS 10229)

763. Climatological Aerological (Upper Air) Reference Data Set

T.R. Karl

(704) 259-0319

\$440,000

The objective of the research is to build a climatological aerological (upper air) reference data set (CARDS) from the radiosonde data archives. A key data set will be provided for climate research requiring atmospheric profiles of temperature, winds, and humidity. The data consist of temperature, pressure, wind velocity, and humidity profiles of the atmosphere. Such data have been measured from twice-daily balloon launches at some 700 to 800 sites around the globe for about 50 years. However, the data are subject to many biases, including the effects of solar radiation on the temperature and humidity sensors. Early data are often uncertain and require extensive correction.

Through six tasks, the research team builds, quality controls, and analyzes CARDS. Task 1 is to acquire the basic data. The project produces a global data set of daily upper-air and concomitant surface synoptic observations using various collections of upper-air and co-located surface observations. The most extensive data set possible is collected. In task 2, the project develops algorithms to flag and correct random errors. These data sets have not been quality controlled in a systematic manner. The team develops a suite of programs to correct for random errors and outliers. The procedures include a range of methods from statistical to physical (impossible temperatures, pressures, etc.). The project makes use of a list of suspect stations noted by the U.S. and European weather centers. A third task is to document station histories and assess the homogeneity of the data. Researchers assess the homogeneity of the data from the upper-air network and implement corrections for biases where appropriate. The station histories provide the information necessary to correct for known biases for sensor and methodology changes and differences over time and between stations (national procedures). Task 4 consists of analyzing the data using basic climate change analysis schemes to help ensure against undetected errors and biases, and provide complete documentation. Task 5 updates the data set, instituting a modest operational program to ensure the integrity of future data. Task 6 is to distribute the data to the research community. The project makes these data sets readily available via the Carbon Dioxide Information and Analysis Center. (RPIS 10289)

National Science Foundation

Washington, DC 20550

Committee on Earth and Environmental Sciences**764. CEES Working Group on Global Change***P.A. Anderson*

(202) 357-7357

\$274,000

The objective of this project is to provide partial support for six activities supported by the Committee on Earth and Environmental Sciences (CEES) Working Group on Global Change (WGCC) and to provide a contingency fund for unforeseen expenses. As a result of this project, a central body is efficiently collecting and distributing legitimate and necessary costs for activities that are shared by agencies participating in the U.S. Global Change Research Program (USGCRP).

The National Science Foundation (NSF) collects funds for CEES and distributes these funds for activities supported by CEES, as agreed by all participating agencies.

The following organizations and activities are being supported: (1) the National Academy of Sciences' Committee on Global Change Research, for activities related to global change; (2) the University Corporation for Atmospheric Research (UCAR), to support the UCAR-sponsored FY 1992 Summer Institutes Program on Global Land Use/Cover Change; (3) printing costs for CEES WGCC documents such as the FY 1992 U.S. Global Change Research Program; (4) the development of software for use in planning, management, and analysis of USGCRP; (5) the Intergovernmental Panel on Climate Change, to support science-related activities involving workshops and meetings of the Response Strategy Working Group; (6) an initial workshop on the concept of a Western Hemisphere Regional Center for Global Change Research; and (7) a contingency fund for unforeseen expenses.

This project also supports the printing costs for global change research documents prepared by the Committee on Earth Sciences of the Office of Science and Technology Policy and printed by Joint Oceanographic Institution, Inc., through a contract with NSF. (RPIS 10498)

Naval Postgraduate School

Monterey, CA 93943

Department of Oceanography, MC68**765. Scientific Development of a Massively Parallel Ocean Climate Model***A.J. Semtner*

(408) 646-3267

\$160,000

The objective of this research is to develop an eddy-resolving ocean general circulation model (OGCM) to run on massively parallel scientific supercomputers. Research is being conducted on (1) heat transport by ocean circulation; (2) the effects of near-surface processes and their model parameterizations on long-term climate simulations; and (3) model resolution requirements for climate modeling studies of ocean circulation. (RPIS 10578)

New York University

New York, NY 10003

Department of Applied Science**766. Climate Evolution with a Coupled Two-Dimensional Atmospheric/Ocean Model***M.I. Hoffert*

(212) 777-4587

\$45,000

An efficient two-dimensional longitude-depth ocean/atmosphere-coupled model is applied to conduct preliminary simulations to guide future three-dimensional studies. This application addresses the development of initialization procedures and subgrid-scale transport parameterizations in ocean general circulation models (GCMs). Ultimately, three-dimensional ocean GCMs are coupled to atmospheric models to perform decade-to-century scale simulations of natural and greenhouse-gas-induced climate variability and change. Computer limits prevent the exercise of these three-dimensional models so that unresolved questions about the initialization and diffusion parameterizations cannot be fully addressed until the next generation of supercomputers is available to the ocean modeling community. This research project is completed within 1 year so that the results are available in a timely matter. The research group uses the two-dimensional model to perform multiple 100- to 1,000-year simulations to examine the various equilibrium states produced by different initial conditions. In addition, the transient response of the ocean is diagnosed as a function of latitude, and diagnostic methods are developed so that similar simulations with other models can be intercompared. This type of intercomparison activity is essential in evaluating model parameterizations and has been used extensively by the atmospheric GCM community. (RPIS 10627)

Oregon Graduate Institute of Science and Technology

Beaverton, OR 97006

Center for Atmospheric Studies**767. Methane Fluxes from Rice Fields in China: Spatial and Temporal Variability and Estimates of Contributions to the Global Budget***R.A. Rasmussen**M.A.K. Khalil*

(503) 645-1121

\$393,000

This project measures the magnitude of methane emission from rice paddy fields, including seasonal and geographic characteristics. This information is needed to understand increasing atmospheric methane concentrations and to predict future atmospheric concentrations. In conducting this project, the Oregon Graduate Institute cooperates with the Chinese Academy of Science (Institute of Atmospheric Physics). To measure the methane released to the atmosphere from rice

paddy fields, a frame is placed in the field as a seal for the enclosure. The enclosure is placed over the plants and a sample is taken quickly, with little or no disruption to the plant or the surrounding surface. Air and soil temperature, growth stage, soil type, fertilizer type, farming practice, etc., are recorded. The measurement technique is portable, easily maintained in the field, and reliable in providing reproducible data; it has been reviewed and field tested extensively over the last 25 years. Four activities are included in the project; the 6-year baseline effort at Tu Zu as well as data collection at additional sites to investigate spatial variability from different climate zones, soil types, farming practices, and rice varieties. These data, along with other methane budget data, are used to estimate seasonal variations and geographic variations in the global methane budget. Further, a mid-Continental background site is being re-established to help assess the atmospheric concentrations of methane and other trace gases. (RPIS 9350)

Rutgers University
New Brunswick, NJ 08903

Department of Meteorology

768. An Evaluation of the Appropriate Land-Surface Resolution for Climate Models

R. Avissar

(908) 932-9387

\$103,000

The research evaluates the resolution at which heterogeneities in land-surface heat and water flux distribution affect the large scale atmospheric structure described by GCMs for climate studies. An analysis is performed of the scale significance and sensitivity of GCMs to surface parameters used in GCM boundary layer parameterizations. A statistically based model of land surface heterogeneity is being developed to describe subgrid scale surface fluxes for integrated grid-scale fluxes in GCMs. The model is tested to examine the nonlinear sensitivities to the 13 parameters that must be specified. A novel differential sensitivity analysis algorithm is employed to reduce the total number of sensitivity runs required from several thousand to several hundred. A mesoscale model is employed to explicitly describe on a fine mesh the parameterized heterogeneities in the subgrid model to test the scheme. (RPIS 10697)

Santa Fe Institute

Santa Fe, NM 87501

769. A Broad Research Program on the Sciences of Complexity

E.A. Knapp

(505) 984-8800

\$79,000

The project objective is to conduct interdisciplinary research and education on the dynamical behavior of complex systems and on the emergence of self-organizing hierarchical systems

from interacting parts. The emergent behavior of the system has far-reaching importance for understanding how nature operates on the macroscopic level. What looks hopelessly chaotic at first may be predictable from understanding the patterns and rules of complex behavior. The Santa Fe Institute (SFI) is an independent, nonprofit research and graduate teaching organization. It is founded on the premise that common principles determine the behavior of complex systems of all kinds, especially systems that learn and adapt. SFI's approach is to understand those principles by studying specific systems ranging from self-learning computer programs to financial markets to the human immune system in that more general context. The Institute has a 50-member Science Board composed of accomplished scholars from disciplines of the physical, biological, informational, and social sciences. Research activities center around the visiting faculty who spend extended time in residence at the Institute. During the year, nine major collaborative working groups were convened. A 10-day workshop took place on the common principles of complex systems. A March 1992 workshop was held on another main focus of SFI, adaptive computation, and there was some emphasis on audification using sonic interface to display complex behavior. (RPIS 10725)

Scripps Institution of Oceanography

La Jolla, CA 92093

Climate Research Division

770. Studies of Ocean Predictability at Decade to Century Time Scales Using a Global Ocean General Circulation Model in a Parallel Computing Environment

T.P. Barnett

A. Miller

(619) 534-3223

\$182,000

The objective of this research is to install a state-of-the-science ocean GCM on a massively parallel scientific computer and to carry out 100-year runs to explore the natural variability of global ocean circulation. Researchers are quantifying the natural variability of the ocean component of the climate system, information that is currently lacking. Secondary products include the experience gained in using massively parallel computers to run GCMs and an understanding of the problems associated with coupling a full atmospheric GCM with an ocean GCM.

The research is divided into five tasks.

Task 1 adapts the ocean GCM acquired from the Max Planck Institute (MPI) in Germany to run on the Intel iPSC/860 parallel supercomputer at the San Diego Supercomputer Center (SDSC). This model has previously been run fully coupled to the MPI atmospheric GCM for a 100-year simulation.

Task 2 develops two stochastic atmospheric forcing models to form an interactive upper boundary for the ocean GCM. One model is constructed from empirical orthogonal functions (EOFs) determined from global atmospheric data sets. "Noise"

resulting from short-term weather events is then filtered to isolate the longer climate scale driving modes. The data sets are then reconstructed with a random stochastic component added to the atmospheric model to reproduce the natural atmospheric variability resulting from the integration of the short-term events. A second model is similarly constructed from atmospheric GCM-derived data.

Task 3 examines the differences in equilibrium states produced in the ocean GCM by the two atmospheric models. This examination determines the problems associated with coupling atmospheric and ocean GCMs, which currently tends to produce a climate that "drifts" away from the observed equilibrium state.

In task 4, the model is run for 100-year simulations using each of the atmospheric forcing models.

Task 5 involves the analysis of three 100-year model runs, the two performed in task 4 and a third simulation in which the model was coupled to a full atmospheric GCM at MPI. Analysis and intercomparison of the three runs allow investigators to determine the time and space scales of natural variability, the mechanisms of model climate drift, and preliminary estimates of the deterministic spatial and temporal limits of predictability of ocean circulation. (RPIS 10547)

State University of New York at Albany Albany, NY 12222

Atmospherics Sciences Research Center

771. Study of Regional Climate Changes

W.-C. Wang

(518) 442-3357

\$326,000

The project's three objectives are to (1) continue development of quality assured data to study long-term regional climate change, (2) use the regional analyses to validate climate models, and (3) understand the differences among the climate models and provide possible improvements via incorporation of advance radiative submodels that include CO₂ and other greenhouse gases. Essential information is provided for developing the regional and global climatic data necessary to document climate change and assess natural variability. Databases are developed against which to test climate models and to improve the basic model parameterizations. The research is organized into four tasks:

(1) General Circulation Model (GCM) Diagnosis. The researchers participate in the two DOE GCM intercomparisons. The SUNY-Albany team uses the National Center for Atmospheric Research (NCAR) GCM called Community Climate Model One (CCM 1). The team conducts model simulations of the 10-year period 1979-1988 for the Lawrence Livermore National Laboratory-led intercomparison, Atmospheric Model Intercomparison Project. Further, the researchers conduct the fixed sea surface temperature experiments for the DOE intercomparison.

(2) Climate Data Preparation. Historical and instrumental climate data sets have been and continue to be collected, examined, quality controlled, and documented for release for the U.S. and for China. The research team completes the documentation and quality control prior to the general release of the data. Further, the group initiates the research necessary to incorporate the proxy (paleoclimate data), historical writings, and the instrumental data into a quantitative time series. Such data can then be used to investigate long-term natural climate variability and validate very long GCM runs.

(3) Regional Climate Changes. From the regional climate database (U.S. and China), the research team examines regional climates, the pattern and timing of the changes, the comparison across regions, and the regional character of the urban heat island.

(4) Relationship Between Large- and Regional-Scale Climate. The research explores how best to bring the data and the models together. For example, surface observations often contain localized characteristics that cannot be modeled by GCMs. The research continues with the NCAR CCM 1 and extends to differently forced climates (i.e., three versions of the CCM 1). In addition, low frequency climate events, such as the El Niño/Southern Oscillation and the Northern Oscillation, are investigated. The regional-scale relationships within the data are compared to the GCM results. These studies assist in validating GCMs and provide information for future predictability studies. (RPIS 10586)

State University of New York at Stony Brook
Stony Brook, NY 11794

Institute for Terrestrial and Planetary Atmospheres

772. Carbon Dioxide-Induced Climate Change

R.D. Cess

W. Hameed

(516) 623-8321

\$427,000

This project aims to (1) intercompare general circulation models (GCMs), documenting physical processes responsible for agreement and disagreement and (2) statistically analyze U.S. and Chinese regional temperature data sets for relationships between large scale and regional climate. This result is an understanding of GCM abilities to represent large scale climate and the relationships between large scale climate and regional climate. The approach taken is a model-to-model and model-to-data intercomparison for GCMs. The current research program concerns the intercomparison and understanding of CO₂-induced climatic warming as indicated by contemporary GCMs. Some 18 GCMs are involved from around the world, including the U.S., France, Canada, West Germany, Japan, Australia, China, the U.K., and the U.S.S.R. An experimental protocol has been developed and is being applied to the model-to-model comparison using a $\pm 2^\circ \text{C}$ sea surface temperature change as the forcing mechanism. The approach assists in diagnosing cloud feedback and cloud forcing and the interactions of ice-snow albedo feedback and clouds in GCMs as a probable cause for GCM disagreements. CO₂ initial forcing and surface radiative balance are also being investigated. Another aspect of the research is devoted to understanding the natural variability in climatic parameters, i.e., the variability that may be affected superposed by the predicted gradually increasing impact of atmospheric CO₂. Analysis is made of subseasonal, annual, and interannual variations in air temperature, precipitation, and sunshine durations in station observations and compared with their simulations in GCMs. The purpose is dual: (1) to quantitatively ascertain the deficiencies of the models so that these may be repaired by the modelers and (2) to demonstrate their regime of success so that useful applications of the presently available models may be made. Climatic data developed by the National Climatic Data Center in the U.S. and the Institute of Geography of the Chinese Academy of Sciences have been used in this project. The project's two tasks together guide the estimation of regional climate change. (RPIS 9355)

University Corporation for Atmospheric Research

Boulder, CO 80307

Climate System Modeling Program

773. Climate System Modeling Program

D. Schimel

(303) 497-1610

\$150,000

This research studies interdecadal climate variability to define the limits of climate predictability. A series of workshops and postdoctoral research fellowships are being produced to ascertain and define the limits and variability of interdecadal climate fluctuations. The Climate System Modeling Program (CSMP) is a unique program sponsored by the University Corporation for Atmospheric Research, the organization that operates the National Center for Atmospheric Research for the National Science Foundation. CSMP draws on intellectual resources throughout the academic and government scientific communities to advance the science of climate modeling. One effort of CSMP addresses the problems of interdecadal climate variability, the time scale of most interest to DOE. (RPIS 10774)

University of Wisconsin

Madison, WI 53706

Space Science and Engineering Center

774. An Experimental Regional Scale Climate Simulation Laboratory

J.R. Anderson

(608) 262-0783

\$100,000

New numerical methods and model formulations are developed for both atmospheric and ocean general circulation models (GCMs) suitable for massively parallel computers. The project develops new algorithms for modeling geophysical fluid dynamics. An evaluation is made of the "local spectral technique" for formulating the atmospheric equations of motion in a GCM. This method is new and has yet to be thoroughly tested. It has promising scaling characteristics for deployment on massively parallel computers. A reformulation of the ocean modeling equations is made using three alternative methods designed to make the numerical solution of the equation set computationally more efficient. The various methods are compared against current methods for efficiency and accuracy. The deployment of these new methods takes place at first on the prototype computer system built at the University of Wisconsin. Ultimately, the methods are installed on CM-5 massively parallel supercomputers. (RPIS 10534)

775. Modeling of Hydrologic and Transport Processes in Relation to Climate Change*D.R. Johnson*

(608) 262-0783

\$107,000

Improved coordinate systems are developed to describe atmospheric dynamics and transport in general circulation models. The project analyzes the accuracy of various coordinate system models used in atmospheric dynamics and transport. Comparison simulations among various models with different coordinate systems are run. The favorable accuracy obtained with isentropic coordinates has been known for some time, but the difficulty in describing the atmospheric boundary layer in models using an isentropic vertical coordinate has been a major obstacle. Recent progress in the development of boundary-layer parameterizations that result in more accurate descriptions of boundary-layer fluxes has made isentropic modeling a feasible alternative to the pressure models. (RPIS 10529)

Global Change: Quantitative Links and ARM

*Intramural DOE Laboratories***Argonne National Laboratory**

Argonne, IL 60439

Atmospheric Physics Section**776. Area-Representative Estimates of Surface Heat Flux for Clouds and Radiation Testbed Sites***R.L. Coulter*

(708) 972-5833

\$200,000

The project develops methods for integrating local and nearly local heat flux estimates made at Clouds and Radiation Testbed (CART) sites to produce an overall estimate representative of the extended CART site areas. It produces transfer functions for estimating representative surface heat flux values for extended CART areas based on direct local measurements of surface heat flux and visualizations of larger scale meteorological features. In general terms, it uses local surface heat flux estimates at many sites within the extended CART domain in combination with area-averaging techniques such as sodar and light scintillation to determine the way in which different categories of surfaces contribute to heat fluxes on a large scale. These large-scale estimates are then used to estimate still larger scale surface heat fluxes that might be inferred from other Atmospheric Radiation Measurement investigations. Visualization techniques are used with surface-based remote sensing (lidar, radar, and aircraft) to determine the

variability across the CART domain due to large-scale structures characteristic of the PBL as a whole. Specifically, prior to the operation of the first CART site, the project develops preliminary methods of averaging surface fluxes of sensible (and latent) heat using existing experimental data. Once the location of the first CART site is selected, it develops a strategy for identifying, locating and using CART instruments to the best advantage for obtaining areal averages of surface heat fluxes. After the first CART site becomes operational, the first experimental task is to carry out measurements of the local surface heat fluxes in parallel with area-averaged measurements and to determine the first-level transfer functions for each surface type. The next task is to obtain areal averages of heat flux across interfaces between different surface types and over regions such as forests and uneven terrain. Finally, using extend-area averaged heat flux measurements in conjunction with CART measurements of secondary parameters that depend primarily on heat flux, the project makes estimates of the full range of transfer functions. (RPIS 5494)

Brookhaven National Laboratory

Upton, NY 11973

Department of Applied Sciences**777. Cloud Albedo Perturbations on Climate***S.E. Schwartz*

(516) 282-3100

\$669,000

This project definitively assesses the enhancement of cloud albedo due to anthropogenic sulfate aerosol and quantitatively evaluates this enhancement. It produces maps of long-time average (e.g., annual) enhancement in planetary albedo due to this mechanism. Historical (100-year) trends are evaluated using emission patterns derived from records of fuel use and fuel sulfur content. Because of the evolution of knowledge relating gaseous sulfur emissions and local cloud condensation nuclei (CCN) and cloud properties, the project is carried out in two stages. Stage 1 consists of the following activities: (1) a systematic search for enhancement of albedo of low altitude marine stratus clouds in the ERBE data due to anthropogenic SO_2 emissions and/or biogenic dimethyl sulfide (DMS) emissions; (2) preparation of a spatially resolved inventory of gaseous sulfur emissions for use in global evaluations of the anthropogenic perturbation of cloud albedo; and (3) preparation of an initial spatially resolved assessment of present and historical anthropogenic enhancement of cloud albedo, incorporating a linear or other simple assumed relation between CCN concentration and modeled SO_4 concentration into general circulation model (GCM) calculations. Stage 2 is a systematic analysis of available data to prepare an improved relation between sulfate aerosol concentration and CCN concentration. The possibility of using satellite measurements of aerosol optical density as a surrogate for modeled sulfate is evaluated. The information obtained from this project permits critical testing of hypotheses linking responses of the Earth's climate to changes in radiative forcing. (RPIS 5386)

Environmental Chemistry Division**778. Radiative Properties of Nonuniform Clouds***P.H. Daum**L.I. Kleinman**G.L. Stephens**(516) 282-7283***\$240,000**

To improve the treatment of cloud radiation interactions and feedbacks in general circulation models (GCMs), this project focuses on the problem of radiative transfer through clouds in the atmosphere. The project combines both theoretical and observational studies of radiative transfer to achieve its objective. Specifically, the project researchers (1) test current parameterizations of cloud radiative transfer processes, (2) assess the effects of cloud inhomogeneities on domain-averaged radiative properties, (3) evaluate methods of retrieval of cloud droplet size distributions and liquid water path from spectral reflectance measurements, (4) perform radiative transfer calculations for clouds with nonhomogeneous microphysical and geometric properties, and (5) develop new methods of modeling radiative transfer through the atmosphere with broken cloudiness. The results of these studies are new and better predictions of cloud radiative transfer in a way that can be directly incorporated into GCMs and related models. (RPIS 5495)

Environmental Measurements Laboratory**New York, NY 10014****Environmental Studies Division****779. Atmospheric Radiation Measurement Program Support***R. Lelfer**(212) 620-3626***\$415,000**

This project samples and analyzes tropospheric aerosol for energy-related and radiatively active pollutants. To accomplish the objective, new, compact, lightweight environmental sampling equipment is mounted on a tethered aerostat sampling platform (TASP), currently operating on Grand Bahama Island. TASPs are large and highly stabilized balloons designed to carry heavy equipment to altitudes as high as 3 km; the equipment is specially designed for mounting on TASP systems. Initial measurements are made with stacked filters and impactor samplers for the purpose of chemical and physical characterization of atmospheric aerosols. These instruments provide samples for trace element, ion chromatographic, and scanning electron microscope analyses and give a detailed picture of the elemental, ionic, and size distribution of the collected aerosol over a long time period. The research effort aims to determine (1) atmospheric transport processes from continental and maritime regions and fluxes to and from the Atlantic Ocean for specific natural and anthropogenic materials and (2) the impact of biological and anthropogenic emissions on

cloud droplet production in a maritime environment. In addition, insights are obtained regarding the transformation of dimethyl sulfide (DMS), a precursor gas emanating from the ocean, into cloud condensation nuclei and cloud droplets. (RPIS 5507)

Lawrence Berkeley Laboratory**Berkeley, CA 94720****Division of Applied Science****780. Modification of Cloud Optical Properties by Aerosols***T. Novakov**(510) 486-5319***\$342,000**

This project experimentally quantitates the links between the optical properties of clouds and atmospheric aerosols such as sulfate and carbonaceous particles. Specifically, the research addresses the question: How do optical properties of clouds respond to changing concentrations of anthropogenic, biogenic, and natural aerosols? The approach to answering this question consists of a combination of field and laboratory experiments. The field experiments are as follows: (1) measure the radiative properties of natural clouds to determine the validity of theoretical predictions of increasing cloud albedo with increasing cloud condensation nuclei (CCN) (particularly sulfate and mineral dust) concentrations; (2) determine the relative impacts of energy-related, crustal, and biogenic aerosols on radiative properties of clouds; and (3) determine the soot content of natural cloud drops so that the possible role of soot particles in decreasing cloud albedo can be assessed. Results obtained from these field studies are being used to design laboratory simulation experiments with the Lawrence Berkeley Laboratory cloud chamber to identify the physics and chemistry of dominant importance in modifying the optical properties of clouds, with special emphasis on enhanced absorption soot-associated clouds. The compilation and analysis of ambient and source emissions data pertaining particularly to soot aerosols aids in obtaining horizontal, vertical, and seasonal variations in global aerosol concentration. (RPIS 5362)

Lawrence Livermore National Laboratory Livermore, CA 94550

Atmospheric and Geophysical Sciences Division

781. Spectroscopic Study of H₂O Absorption in the 8- to 14-Micrometer Atmospheric Window: Measurement of New Line and Continuum Parameters and Investigation of Far-Wing Phenomena

T.J. Kulp

(415) 423-7839

\$180,000

An accurate characterization of atmospheric water vapor absorption in the infrared transmission window at 8- to 14- μ m is essential to reliable modeling of the global energy balance. To this end, this project performs laboratory measurements primarily using diode laser absorption spectroscopy with a long path-length absorption cell. First, the line parameters of as many lines as possible in and around the window region are quantified at various temperatures and pressures. These measurements are compared with the results of HITRAN calculations. Next, the dependence of the continuum absorption of water vapor on both temperature and wavelength in the window region is quantified; these results are compared with previous measurements where possible. The feasibility of using double resonance techniques to study individual, isolated rovibrational lines to characterize the far-wing absorption in water vapor absorption is evaluated. Finally, measurements on molecules that have simpler band structures than water are taken to allow observations of line shapes under more isolated conditions than is possible with water. The project provides (1) data to fill in the gaps in the present empirical database regarding the 8- to 14- μ m line and continuum absorption, and (2) fundamental data on far-wing line structure that contributes to an improved theoretical understanding of the water vapor continuum. (RPIS 5424)

782. The Role of Aerosols and Cloud Microphysics in Climate and Climate Change

J.E. Penner

(415) 422-4140

\$318,000

This project uses data analysis, together with a global model, to quantify the effects of aerosols and clouds on the radiative budget of the earth and climate. The project examines available data in comparison to the predictions of a three-dimensional global model for aerosols and clouds. Data on individual sulfur species, aerosol concentrations, elemental carbon concentrations, and cloud microphysical properties are used. Comparisons of the global model with long-time series data for single stations or comparisons to satellite data are emphasized in this work; however, comparison of the model with more short-term episodic data also provides valuable insight and allows even short-term data to be folded into the analysis. In this way, the data from a single station or even a single event—can be extrapolated to the globe to determine the global impact. The project's end product is quantification of the link among aerosols, cloud microphysical properties, and climate. (RPIS 5387)

Los Alamos National Laboratory Los Alamos, NM 87545

Earth and Environmental Sciences Division

783. Remote Sensing of Surface Fluxes Important to Cloud Development

F. Barnes

W.E. Clements

W.B. Porch

(505) 667-4933

\$300,000

This project is designed to determine the connection between rates of cloud formation and upward fluxes of water vapor and heat from the surface. The project addresses the Atmospheric Radiation Measurement (ARM) Program goals of relating local measurements to values appropriate to grid scales of general circulation models (GCMs) and interpreting GCM results in terms of local meteorology. An integrated measurement program studies the patterns of surface fluxes of water vapor and heat for clouds and radiation testbed (CART) sites under a full range of climatic conditions. These measurements are used to evaluate the influence of the upward fluxes on the rate of cloud formation and radiation transport. Combinations of remote-sensing instrumentation are used to detail the three-dimensional structure of the lower atmosphere. Observed patterns in the atmosphere are correlated with both surface vegetative and terrain pattern and inhomogeneities in the cloud layer. Flux estimation tasks are to (1) determine the spatial and temporal variabilities in heat and water vapor flux rates and relate these to variations in the radiative balance above the site and (2) map the time-dependent vertical distribution of water vapor from the surface to the cloud layer. Cloud and surface characterization tasks are to (1) monitor cloud cover and radiative transfer properties using lidars, a multispectral digital camera with real-time calibration from star irradiance, and satellite imagery; (2) establish topography and terrain features using digital maps, measure standard ecological features; and (3) perform surface albedo measurements using instruments mounted on aircraft and/or remotely controlled platforms. The analysis and modeling tasks are to (1) examine the scaling characteristics of the evaporative fluxes over a variety of ranges up to the subgrid scale of mesoscale models and the grid size of GCM models; (2) correlate the flux fields over a CART site with cloud characteristics and dynamics over the site and downwind from the site; and (3) based on modeling studies, evaluate the feedbacks between the surface and the atmosphere that contribute to cloud formation over a site or downwind. (RPIS 5498)

784. Ocean Cloud/Climate Linkage Study*W.M. Porch**(505) 667-0971***\$250,000**

This experiment improves understanding of how marine stratocumulus clouds respond to changes in atmospheric composition and atmospheric warming and thus affect climate. Specifically, the results of this experiment are being used to improve ocean cloud parameterizations in climate models and ocean data stratification for satellite cloud trend studies. This research aims at determining the effect of heating and aerosol nucleation on marine stratocumulus clouds by studying the effect of large ships on cloud development and albedo. Experiments are being conducted under meteorological conditions favorable to ship-trail development-i.e., in ocean regions where clouds are particularly sensitive to anthropogenic influence. Large ships with the potential for ship-trail formation are followed by research vessels (ships and/or aircraft) equipped to probe and sample the trails. The results are being used to test and improve dynamic and aerosol microphysics-based numerical cloud models. The results from the experiments and model studies are being used to provide a matrix of sea surface temperature and marine boundary layer conditions occurring during high-resolution-image satellite overpasses of these cloud-sensitive regions. This matrix aids in the interpretation and development of trend analysis of cloud fraction, albedo, and atmospheric composition. (RPIS 5363)

Institute of Geophysics and Planetary Physics**785. Interfacing Between a Hierarchy of Numerical Models in the Atmospheric Radiation Measurement Program***C.Y.J. Kao**(505) 667-9226***\$400,000**

This project is designed to establish the relationship between the collective effects of clouds from cloud-scale simulations and the mean variables resolvable in general circulation models (GCMs). The project is consequently developing methodologies for interfacing and data assimilation from a hierarchy of numerical models. To do so, the project uses a hierarchy of models ranging from GCMs to mesoscale models to cloud models to develop methodologies for data assimilation among the models as well as between models and field observations. The large scale results of GCM calculations are used to drive (or guide) mesoscale models that subsequently provide input to the cloud models. The collective effects of clouds are then derived from the detailed processes associated with the individual components of the cloud system and, in turn, related to the mean variables in the GCMs. GCM parameterizations are thus tested extensively against detailed, three-dimensional process models. The data assimilation methodologies allow Atmospheric Radiation Measurement (ARM) Program measurements, augmented with "numerical field experiments," to be incorporated into the models in a dynamically consistent way so as to increase the reliability and universality of GCM parameterizations. (RPIS 5497)

786. Cloud Parameterization in Climate Models*C.Y.J. Kao**(505) 667-9226***\$236,000**

The project uses advanced measurements in the Atmospheric Radiation Measurement (ARM) program to investigate improved parameterizations of low level stratus or stratocumulus, penetrative cumulus, and high level cirrus clouds in general circulation models (GCMs), including evaluation and validation. Data from state-of-the-art ARM instrumentation are used to develop a cloud parameterization technique with the capability to parameterize low level stratus/stratocumulus, penetrative cumulus, and high level cirrus with new physical schemes for improvement of cloud simulations in GCMs. The principal tools are the physically based Arakawa-Schubert scheme for penetrative clouds and the Sundqvist scheme, which is refined by the incorporation of diffusion processes derived from a second-order turbulence approach. Clouds are more accurately parameterized as both the advanced measurements of ARM and the future high resolution climate models continue to improve the resolution of temporal and spatial fluctuations. Performance analysis results are used to iteratively evolve improvements in parameterizations. (RPIS 5635)

National Renewable Energy Laboratory**Golden, CO 80401****Photovoltaics Division****787. Atmospheric Radiation Measurements Program Support***R.L. Hulstrom**(303) 231-1220***\$50,000**

Preliminary technical planning is being conducted under this project for the radiation measurements portion of the Atmospheric Radiation Measurements (ARM) Program. The long-term goal of the radiation measurements effort is to develop, deploy, and integrate radiometric instrumentation at ARM research sites and provide a transition to the groups responsible for operation of the equipment and data system(s). The project involves the clouds and radiation testbed (CART) portion of the ARM Program, which serves as the program's experimental framework and infrastructure. CART includes fixed experimental sites, a mobile complement of instrumentation, and a series of focused campaigns aimed at particular scientific issues. A list of candidate radiometric instruments for CART is generated by a group of experts who review the ARM Program's requirements, experimental design, and preliminary experiment catalog. The list contains generic names (e.g., shortwave spectral radiometer), instrument names (e.g., spectroradiometer), and variables measured (e.g., radiance and irradiance). This list is supported by complete instrument descriptions and includes a recommendation for instruments essential to meet the ARM mission, a set of options for meeting specific measurement requirements, suggested calibration protocols for each instrument, and a list of

instruments recommended beyond the basic complement. This list, the associated descriptions, and other information are used to prioritize the acquisition and deployment of ARM radiometric instrumentation. Project activities also include work with the ARM Program and Instrument Team to ensure that ARM radiation measurements and instrumentation allow the ARM mission to be completed. This activity includes initial investigations of calibration methods and analyses of total measurement uncertainty for each candidate radiometric instrument. (RPIS 5380)

Oak Ridge National Laboratory Oak Ridge, TN 37831

Environmental Sciences Division

788. Database Support to Assist in Quantifying the Link Between Changes in Atmospheric Composition and Climate Change

R. Cushman

P. Kanciruk

(615) 574-0390

\$525,000

This project aims to provide quality assured data sets for the detection of long-term climate trends that may be related to changes in atmospheric composition. The objective is a numeric data package based on a quality-assured long-term climate data set (including monthly surface air temperature, precipitation, and atmospheric pressure values) that is global in spatial extent. In this project, data from the World Weather Records and Monthly Climate Data for the World are (1) supplemented, to increase spatial coverage, with additional data sets; (2) quality assured and corrected, where possible, to remove erroneous data or adjust for inhomogeneities such as station moves; (3) documented; and (4) packaged for distribution as a numeric data package. Working under the auspices of existing U.S.-U.S.S.R. bilateral agreements, researchers are identifying existing climate-related data sets residing in the Soviet Union. Those sets most important to quantification of the link between radiative balance and atmospheric temperature are being acquired. These data sets are quality assured (i.e., erroneous data is removed), documented, and packaged for distribution as a numeric data package.

Also, climate researchers around the world are being surveyed to identify the most important extant climate-related data sets for quantifying the link between radiative balance and atmospheric temperature. A workshop is being held to rank the identified data sets in terms of programmatic needs and schedules. (RPIS 5364)

Instrument and Controls Division

789. Widely Deployable Low Cost Radiometer for the Atmospheric Radiation Measurement Program Extended Observing Stations

R.C. Kryter

(615) 574-5561

\$318,000

Under this project, a customized radiometer is being designed, developed, and demonstrated for the Atmospheric Radiation Measurement (ARM) Program extended observing stations. The radiometer developed is superior to presently available instruments and is less costly to deploy, calibrate, and maintain. The project's technical approach is based on (1) optimizing sampling of the solar spectrum to provide an estimation covering the full solar spectral curve (300 to 1,100 nm) from a limited number of measurements; (2) making maximal use of very large scale integration and computer-generated hologram technologies to realize a more reliable, maintainable, and rugged instrument while simultaneously reducing cost per unit; and (3) applying data fusion concepts to best advantage so as to provide capability for dynamic adjustment of measurement parameters, remote calibration, and fault detection. To do so, a solar spectrum sampling scheme, based on general circulation model (GCM) needs and estimation theory, is developed to arrive at a canonical spectral representation from a relatively small set of samples. Data fusion algorithms and concepts are developed. The photodetection arrays, radiometer circuitry, and computer-generated hologram are designed, simulated, fabricated, and tested. The radiometer packaging is designed and fabricated, and the customized radiometer unit is laboratory and field tested. (RPIS 5499)

Pacific Northwest Laboratory Richland, WA 99352

ARM Program Office

790. Atmospheric Radiation Measurement Program

G.M. Stokes

(509) 375-3816

\$13,888,000

The objective of this project is to improve the performance of general circulation models of the atmosphere for the purpose of global and regional climate prediction. The Atmospheric Radiation Measurement (ARM) Program focuses specifically on two aspects of that improvement: the treatment of radiative transfer and related models in general circulation models (GCMs) under clear sky, general overcast, and broken cloud conditions; and the parameterization of cloud properties, cloud formation, and cloud maintenance in GCMs.

Task I

This research provides for the management of the ARM Program and the development of the experimental infrastructure of that program, known as the Cloud and Radiation Testbed (CART). The ARM experimental framework provides

a basis for detailed testing and verification of the modeling of subgrid processes in GCMs, the ability to rapidly deploy experiments to the field, and a strong coupling to the scientific goals of the program.

The ARM Program is managed from the ARM Project Office, located at the Pacific Northwest Laboratory, and consists of three distinct entities: the Science Team, the Instrument Development Program (IDP), and CART. The Project Office provides central planning and management for the ARM Program, support of the DOE/OHER Environmental Sciences Division's activities, and coordination of the ARM Program activities with related technical activities in other agencies and countries.

The Science Team conducts approved research projects; provides basic guidance for the selection of sites, common modeling activities, and instrument selection; and sets the scientific direction of the ARM Program.

IDP provides a program for the long-term high risk development of critical technologies that will be of long-term interest to ARM. It will also provide a directed instrument-development activity when an instrument must be developed to meet a need that cannot be met by other means.

CART is the basic experimental infrastructure for the ARM Program. CART itself consists of several permanent observing stations; an ability to support intensive campaign activities; and a data system that acquires CART data and supplementary data from outside sources, processes that data, archives appropriate data, and provides requested data to individual members of the Science Team.

The field sites are being established by Site Program Managers selected from within the DOE national laboratories. Directly supporting this activity and the Science Team are interlaboratory teams, headed by a principal investigator from one of the DOE national laboratories. Interlaboratory teams address program needs relative to instruments, data management, Science Team experiment support, site operations, and campaign coordination.

Subtask I(a)

This research manages DOE-funded development of field-hardened instrument designs suitable for replication and installation at CART sites as cost-effective, turnkey instruments. More complex instruments developed under IDP are being used on a campaign basis.

Instrument development projects are funded for 2 to 3 years in order (1) to verify the atmospheric measurement concept; (2) to upgrade existing instrumentation to better meet ARM measurement requirements; and, in some cases, (3) to deliver field-hardened instrumentation for permanent installation at a CART site.

Task II

This research provides for the implementation and operational management of the southern Great Plains site, for the initiation of site implementation planning for the Tropical Western Pacific Ocean and North Slope of Alaska sites, and for general site operations planning and coordination activities within the infrastructure of ARM.

The Site Program Managers plan and direct the overall implementation of each of the sites with support from the Site Operations Team. The Site Operations Team develops the initial site operations plan for each site, trains operations personnel during the site deployment, and ultimately transfers the site, its associated equipment, and the maintenance of the site operations plan to the Site Operator and the Site Program Manager.

Task III

This research manages and develops algorithms for producing measurements required by Science Team members and developing, in conjunction with Science Team members, detailed experiment designs that define their measurement requirements.

Identification and development of procedures to meet the measurement needs of the Science Team is a function of the Experiment Support Team. Based on four general measurement strategies that encompass and describe the scientific basis of the various Science Team projects, procedures—including specific algorithms—are produced for each requested measurement. These fundamental algorithms are implemented in the Experiment Center at Pacific Northwest Laboratory and are used to derive measurements requested by the Science Team that have a specified space and time resolution. An Experiment Support Team member meets with each principal investigator to define specific measurement requirements. In addition to developing measurement algorithms, the Experiment Support Team is responsible for developing, in conjunction with the Science Team, quality measurement experiments that compare two or more measurement data streams as part of the data quality control process.

Task IV

In this project, researchers manage and execute ARM infrastructure activities concerning instrumentation and the identification, installation, and implementation of instrument systems.

Argonne National Laboratory leads an interlaboratory instrument team whose tasks are (1) to identify and evaluate technologies for possible incorporation in observations systems of CART; (2) to develop the initial operational and calibration protocols for each equipment item before transferring it to individual ARM site operators; and (3) to provide technical information to support the acquisition of instruments.

Task V

In this work, researchers manage and operate the ARM infrastructure activities associated with the design, development, implementation, and deployment of an integrated data system for the acquisition, quality assessment, analysis, distribution, and archiving of ARM data.

A multilaboratory team has continued the top-down design of the system and implemented the first elements of the system. The incremental implementation and deployment of the system allow for adapting the system to changing requirements as the CART site is deployed and operated.

Task VI

This project manages campaign identification and coordination activities within the infrastructure of ARM, and potential relationships between ARM and other experimental programs are identified.

Campaign planning and coordination is a centralized activity within the program and may be embodied in a campaign committee. This committee acts as the primary point of contact between CART and the Science Team, or between ARM and the external research community, for support requests to include ARM capabilities in campaign planning. In addition, the committee periodically reviews CART observational data and assesses whether a targeted campaign may be necessary to meet specific ARM research objectives. (RPIS 5342)

Atmospheric Sciences Division**791. Point-Area Relationships for Global Climate Modeling***J.C. Doran*

(509) 376-4734

\$420,000

This project develops procedures for extrapolating local measurements of radiation and heat flux to larger areas representative of a general circulation model (GCM) grid cell. Work is conducted at carefully selected sites under well-defined, relatively stationary meteorological conditions and over surfaces that emphasize the importance of subgrid scale variations in fluxes. These sites are necessary to test preliminary approaches, identify and correct problems, and analyze initial findings. Based on these findings, methodologies that are more general in scope and applicability developed and applied to specific clouds and radiation testbed (CART) sites. Project tasks are to (1) develop interpolation-extrapolation methodologies to derive areal average flux values from point measurements, (2) collect surface and aircraft data and examine and improve formulations for GCM grid-sized areas, and (3) use mesoscale numerical models as a tool for systematic testing of the effects of surface inhomogeneities. The resulting products are improved parameterizations of surface heat fluxes, for use in GCMs and related models, which account for subgrid scale variability arising from inhomogeneous surface properties. (RPIS 5501)

792. Network-Based Solar and Meteorological Characterization of Cloud-Radiation Effects in Global Climate Modeling*N.S. Laulainen*

(509) 376-4155

\$275,000

Clouds mask about half the earth's surface at any given time; therefore, it is important to know how clouds interact with outgoing longwave (infrared) and incoming shortwave (solar) radiation to regulate the heating of the planet. To better understand how these climatically opposed effects vary in time with cloud type and structure and, to a limited extent, with geography, this project establishes a nine-station regional

network in the eastern United States. Each station is equipped with standard instruments for measuring ambient temperature, total precipitation, and relative humidity. Observations of diffuse horizontal, total horizontal, and direct normal solar irradiance are the primary solar measurements. All three solar radiation components are measured with the same sensor for increased stability. Upward-looking horizontal infrared and local surface albedo data supplement these data and aid in their interpretation. Of greater utility, perhaps, than the solar observations themselves are the climate-sensitive parameters derived from them: cloudiness, cloud optical depth, cloud type (to some extent), and aerosol optical depth and its wavelength dependence. The study goals are (1) to use ground-based measurements in concert with Earth Radiation Budget Experiment (ERBE) results to characterize cloud radiative forcing for a variety of cloud types and structures over a limited geographical area, (2) to track changes in cirrus frequency and optical depth, and (3) to track changes in aerosol optical depth and its wavelength dependence. Accomplishment of these goals shows (1) how the atmosphere, and especially clouds, forces the "top-of-the-atmosphere" infrared and solar radiation to observed values; (2) whether cirrus clouds are increasing in the nonovercast sky condition; and (3) whether the tropospheric aerosol burden is changing with time and how it affects a cloudy sky albedo. (RPIS 5388)

793. Photometric Studies of Clouds from an Atmospheric Radiation Measurement Program Site*C.D. Whiteman*

(509) 376-7859

\$150,000

This project enables vertical profiles of radiative fluxes in the lower 1.5 km of the atmosphere to be acquired inexpensively and on a routine basis. The system comprises three subsystems: a commercial tethered balloon platform modified as necessary, modified net radiometers, and the radiometer mount that maintains the radiometers in a level attitude under ambient wind conditions. The project consists of three phases. Phase I, initial design and prototyping, involves: (1) theoretical calculations of the effects of the balloon on radiation measurements and the effect of nonlevel radiometers; and (2) the design, fabrication, and testing of a working prototype using the gimbal mounting system. Phase II involves development and interfacing which: (1) uses lighter materials and refined packaging to achieve a low weight, high reliability flyable package and (2) interfaces the electronics package with the existing tethersonde input signal requirements. In Phase III, the system is field tested. Field testing tasks are to (1) acquire and compare profiler data with data from instruments located on a 300-m tower at the Boulder Atmospheric Observatory and (2) deploy the profiler at a clouds and radiation testbed site and develop routine sounding procedures that could be used by inexperienced operators. (RPIS 5502)

Earth and Environmental Sciences Center

794. Development of a General Circulation Model Stratiform Cloud Parameterization

S.J. Ghan

(509) 376-3161

\$178,000

The project develops and tests a cloud microphysical model that distinguishes cloud water and ice and captures the subgrid distribution of the bulk properties of clouds in general circulation models (GCMs). The new parameterization represents the distribution of bulk cloud properties that are most significant to radiation algorithms in GCMs. A bulk cloud microphysics model developed for cloud simulations is adapted for application to the full lifecycle of stratiform clouds. Cloud droplet number is represented as a prognostic variable dependent on aerosol concentrations and vertical motion. Other prognostic variables to be addressed are cloud liquid water, cloud ice, and ice crystal number density; subgrid scale distributions of cloud water and ice are represented. Cloud variables are parameterized for use in GCMs. The parameterizations are evaluated in "single-column" mode using ARM observations, and in a GCM. Verification is achieved through comparison with observed radiative fluxes, cloud distribution, and vertically integrated cloud liquid water. (RPIS 5636)

795. Parameterizations for Integrals of Radiation's Effects on Clouds, Surfaces, and Stabilities

W.G.N. Slinn

(509) 376-4606

\$80,000

This project develops scientific concepts underlying the integral approach to the use of the clouds and radiation testbed (CART) for significantly reducing the uncertainties in current parameterizations of important radiative transfer processes for use in general circulation models (GCMs) and related models. Project outcomes are specific methods and measures for applying the integral approach to improving parameterizations of radiative transfer processes associated with cloudy skies and inhomogeneous surfaces. The technical approach finds empirical solutions to radiative transfer problems using integral measures rather than differential measures. Because nature integrates over all details and only highly integrated approaches can be effectively used in GCMs, this methodology offers a unique approach to the design of experiments and campaigns. The project focuses on (1) identifying those variables that represent nature's integrations of many complicated variables and processes and (2) developing the concepts and methods for incorporating such variables into improved parameterizations that will characterize radiation's effects on clouds and stability. (RPIS 5500)

Sandia National Laboratory

Livermore, CA 94551

796. Laser Remote Sensing of Water Vapor

M. Lapp

S.H. Melfi

(415) 294-2435

\$650,000

In the project, Raman lidar technology is extended to enable vertical profiles of water vapor to be obtained both day and night. The end product is a prototype Raman lidar system with sufficient accuracy, reliability, and automation for inclusion in the clouds and radiation testbed (CART). Project tasks consist of the following: (1) identification and definition of the detailed characteristics needed for a day/night-capable water vapor probe at a CART site; (2) development of a complete optimization analysis-instrument performance model, including selection of the optimum laser wavelength; (3) design and fabrication of the daytime probe upgrades; (4) supporting research and development focusing on a Raman shifter for changing the wavelength of the candidate laser source, more accurate determination of absorption cross sections for potential beam-absorbing gases, careful investigation of potential laser-induced fluorescence interference, and user-friendly data processing software; (5) integration of the daytime probe upgrades into an existing Raman lidar system; (6) field testing and model validation; and (7) conceptual design and costing of a CART-ready system. (RPIS 5503)

Center for Combustion Research and Technology

797. Passive Cloud Dynamics Measurement - A Flow Field Registration Approach

P.W. Kegelmeier, Jr.

(510) 294-3016

\$115,000

A novel approach to the passive measurement of cloud bottom heights, cloud geometries, and cloud dynamic properties is developed using sequential cloud images. (The technique is based on exploiting the characteristics of optical flow fields.) The project develops, implements, and determines the accuracy of the flow-field method for producing the measurements. Computer image processing algorithms are developed to be suitable for extracting cloud bottom heights, cloud geometries, and cloud dynamic properties using cloud images acquired with a whole-sky-imager (WSI). WSI digital data is integrated with simultaneously acquired ceilometer data to determine WSI sequences for which cloud bottom height groundtruth is available. The primary effort is to develop a technique using optical flow fields to extract cloud base height, methodology, and dynamic properties. An algorithm for extracting optical flow fields from the cloud images is also under development. Cloud motion and geometry correction issues necessary to provide a common frame of reference for the flow fields are addressed. New, multiseasonal, time-dependent

digital cloud imagery is used to investigate the extension of the flow field and registration algorithms to the measurement of cloud shape, size, and extent. Subsequently, the technique will be extended to monitoring the complete cloud life cycle, from inception through persistence and break-up. (RPIS 5637)

Global Change: Quantitative Links and ARM

Offsite Grants

University of Alaska Fairbanks, AK 99775

Geophysical Institute

798. The Effect of Cloud Microphysics on Climate Sensitivity

K. Stamnes

(907) 474-7368

\$80,000

This research develops cloud radiative parameterizations based on liquid water content and cloud drop-size distribution. These parameterizations are used in a radiative-convective model to assess the impact of potential changes in cloud microphysics associated with greenhouse warming on cloud/radiation feedback and thereby climate sensitivity. The research provides a more realistic treatment of clouds in climate models by developing methodologies based on cloud microphysics. Cloud feedbacks comprise a critical problem for quantitative modeling of the atmospheric response to enhanced trace gases, the current understanding of which is very poor. This research focuses on the effects of potential changes in cloud micro-physics due to a greenhouse warming on the radiative energy budget of the atmosphere. The cloud liquid water content and drop-size distribution is used to define cloud radiative properties. Reliable and efficient parameterization of scattering and absorption/emission by cloud droplets is developed. This provides a better understanding of the role of cloud microphysics in the determination of cloud radiative properties. A radiation model including these cloud parameterizations is used to investigate seasonal and latitudinal effects of the influence of cloud microphysics and liquid water content. A detailed, one-dimensional radiative-convective model is used to study the role of cloud microphysics in the determination of cloud radiative properties. This model is used to obtain first estimates of the surface temperature response to potential changes in cloud microphysics associated with greenhouse warming. It is also used to assess how cloud droplet size influences cloud/radiation feedback and thereby climate sensitivity. The climatic implications of changes in cloud microphysics in one- and multidimensional climate models is assessed. (RPIS 10314)

University of Colorado Boulder, CO 80309

Cooperative Institute for Research in Environmental Sciences

799. Thermohaline Circulations and Global Climate Change

H.P. Hanson

(303) 492-1227

\$164,000

The project objective is to investigate the sensitivity of the thermohaline circulation of the North Atlantic to changes in surface forcing that may be expected with CO₂-induced global warming. The project examines a potentially important feedback between the rate of CO₂ uptake by the ocean and the production of cold water in the North Atlantic and assesses the role of this feedback in the rate of global warming. The approach begins with simple sensitivity studies to address the role of hydrological forcing versus thermal forcing in the model. The work then investigates the role of mesoscale eddies in the annual cycle of mixed-layer deepening and retreat. Salinity, topography, and realistic coastlines are explicitly included in the calculations. The feedback process is addressed and the climate sensitivity to the feedback assessed from the model. The numerical experiment tackles the important problem of ocean-climate interactions. It complements ongoing eddy-resolving calculations of circulation in the North Atlantic being made for the World Ocean Circulation Experiment (WOCE), which may provide new insight about high latitude ocean circulation lacking in coarse-grid Ocean General Circulation Models. This research improves quantitative understanding of the long-term changes in global temperature that may be expected to occur with increasing concentrations of CO₂ in the atmosphere and improves estimates of the ocean's ability to dissolve CO₂. Because the research involves the behavior of the ocean on time scales of decades, no existing data sets are appropriate for developing this understanding, and the future data collection efforts are unlikely to be sufficiently timely to provide the needed information. Numerical modeling is, therefore, required. (RPIS 10307)

Colorado State University Fort Collins, CO 80523

Department of Atmospheric Sciences

800. Monitoring the Response of the Upper Troposphere/Lower Stratosphere to a Greenhouse Gas Scenario

S.K. Cox

(303) 491-8594

\$179,000

The project objective is to develop a system capable of simultaneously monitoring the increased CO₂ concentrations and signals of global warming using radiometric methods. The data provide observations necessary to advance climate

models and assist in linking the processes leading from increased greenhouse gases to global climate change. The research attempts to monitor three main components of a climate change scenario. The method, which pays particular attention to the role of changing amounts of CO_2 , is based on field measurements of the downwelling radiation field using a moderate resolution interferometer. By examining the relative changes in the zenith viewed atmospheric radiance over time and the ratios of the radiance at two observation angles, researchers can extract information on the concentration of CO_2 and the resulting changes in CO_2 emission temperatures. A more detailed analysis of the data would provide an estimate of variation in water emission and cirrus cloud cover as well. Monitoring these three climatic modulators substantially enhances the ability to establish the linkages of increasing CO_2 concentration to climate change. (RPIS 10234)

801. The Use of Atmospheric Radiation Measurement Data To Test an Improved Parameterization of Upper Tropospheric Clouds for Use in Climate Models

D.A. Randall

(303) 491-8474

\$164,000

The project develops improved parameterizations of upper tropospheric cloudiness by improved understanding and modeling of the coupling between upper-tropospheric stratiform anvil and cirrus clouds and deep cumulus convection, and determines the effect on the atmospheric energy balance by the distribution of such clouds, including the effect of energy redistribution through latent and sensible heat transport and release. Parameterizations are improved for upper tropospheric cloudiness for the three-dimensional Colorado State University (CSU) general circulation model (GCM). The approach being taken exploits the evolution of three fundamental models and modeling approaches; namely, the CSU GCM, a one-dimensional version of the CSU GCM, and the UCLA cumulus ensemble model. Data acquired by the Atmospheric Radiation Measurement (ARM) Program at the field measurement sites are used to drive the UCLA and CSU one-dimensional models; predictions of those models are compared directly to later observations to evaluate the performance of the models. This approach uses existing models to address: (1) a prognostic approach for the parameterization of cloud formation and dissipation, including grid-cell average cloud water and its relation to the fractional cloud amount and (2) the development and testing of improved diagnostics for the parameterization of cloud formation and dissipation, including the refinement of current semi-empirical correlations for stratiform and convective clouds as functions of relative humidity and cumulus mass flux, respectively. (RPIS 10520)

Defense Advanced Research Projects Agency

Arlington, VA 22209

Advanced Technology

802. A JASON Study of Selected Topics for DOE

J.N. Entzminger

(703) 883-7382

\$85,000

The objective of this project is to bring new scientific expertise, understanding, insights, and critical faculties to the problems faced by the U.S. Government. The project results include a briefing to the Director of the Atmospheric and Climate Research Division, DOE, and other DOE managers on study results and methods. JASON reviews for the Director of the Atmospheric and Climate Research Division the technical progress being made on two programs, the Atmospheric Radiation Measurement (ARM) Program and the Computer Hardware, Advanced Mathematics, and Model Physics (CHAMMP) Program. To provide a comprehensive review of these programs, scientists outside of JASON are being used in addition to select members of the JASON group. (RPIS 10714)

University of Denver

Denver, CO 80208

Physics Department

803. Development of a Short Wavelength Infrared (SWIR) Solar Spectral Radiometer for the Atmospheric Radiation Measurement Program

D.G. Murcray

(303) 871-2627

\$98,000

The project develops and tests a highly accurate, absolutely calibrated, spectral radiometer capable of measuring solar radiance in the 0.8 to 5 micron spectral interval. The project combines the compactness of a moderate resolution (one wavenumber) Fourier-transform infrared interferometer (FTIR) and state-of-the-art electro-optic components with the availability of National Institute of Standards and Technology reference calibration sources to achieve the design goal of a few percent absolute radiometric calibration. A prototype FTIR radiometer system is suitable for the acquisition of sky radiances in the 0.8 to 5 micron spectral region. An existing University of Denver moderate-resolution FTIR interferometer system is modified to obtain data in the short wavelength region. The project develops a high temperature (>1500 Kelvin) black-body radiance source and purchases a National Institute of Standards and Technology NIST-referenced radiance source calibrated from 0.8 to 6 microns. The interferometer system is calibrated using the high temperature blackbody source and the NIST-referenced source. Observations are made from Mauna Loa (or Mt. Evans) using this system on a number of clear days and from these observations construct modified Langley plots to determine the absolute spectral radiance of the sun in the

spectral interval from 0.8 to 5 microns. The onsite data are regularly referenced to the black body source and periodically against the NIST-referenced standard. Based on these studies, one or more short wavelength, moderate resolution solar interferometers are constructed to measure the incoming direct solar radiation for the Atmospheric Radiation Measurement Program Cloud and Radiation Testbed site. (RPIS 10607)

Desert Research Institute

Reno, NV 89506-0220

Atmospheric Science Center

804. Linkage of Anthropogenic Aerosol to Clouds and Climate

J.G. Hudson

(702) 677-3119

\$105,000

The objective of the research is to quantitatively establish the definition of cloud condensation nuclei (CCN). The research provides a basis for separating the relative effects on cloud microphysics of natural and anthropogenic CCN. It defines the nucleus supersaturation range appropriate to stratus clouds and the relative efficiency of nuclei to active cloud formation. Clouds and cloud radiative properties are important factors to study. Establishing the definition of cloud condensation nuclei provides a distinction to be drawn between the overall role of natural and manmade nuclei in cloud formation. The result is a determination of the linkage between global air pollution and cloud microphysics which may allow realistic estimates of this possible anthropogenic effect on cloud radiation balance and climate—key to the quantitative links research program. A measurement program for CCN, based on proven techniques, is carried out. Cloud formation, radiative properties, and precipitation characteristics depend on the number, size, and chemical properties of CCN. This effort collects data on the size and number. CCN are measured using the instantaneous CCN spectrometer previously developed and proven by the principal investigator. The approach provides a detailed CCN spectrum over the entire range of interest to cloud physics. The nuclei actually active in cloud formation can be subtracted out from the total aerosol. Identification of the CCN can then lead to determination of the cloud activation efficiency over a given size range and other radiative properties of the CCN. Surface and aircraft measurements are used to collect CCN/aerosol samples for analysis. Wet and dry aerosols are separated by electrostatic means, and direct chemical as well as water solubility properties of the materials are determined. The analysis helps to define the differences between natural and anthropogenic CCN. (RPIS 10290)

Illinois State Water Survey

Champaign, IL 61820

805. Determining the Chemical Composition of Cloud Condensation Nuclei

A.L. Williams

(217) 244-0373

\$425,000

The project objective is to develop the instrumentation and methodology to determine the cloud condensation nuclei (CCN) chemistry in ambient air samples. The research produces data for characterization of CCNs and cloud microphysics in general circulation models. The role of clouds in climate change is increasingly recognized as important because of their radiation properties. The underlying CCN spectrum largely determines the cloud droplet spectra and influences the resulting cloud radiation properties. An understanding of the CCN chemistry is critical to realistic analysis of the role of clouds in climate warming scenarios. This work develops the appropriate instrumentation and methodology to determine the CCN chemistry in ambient air samples. The experimental approach is to draw air continuously into a flow-type thermal diffusion cloud chamber to form droplets on the CCN at precisely controlled supersaturations, and to remove the droplets immediately from the flow stream to minimize contamination. The droplets are then collected on a filter medium for analysis. Microgram amounts of CCN material are collected. Chemical analysis is attempted using liquid ion chromatography and atomic adsorption techniques. Other techniques investigated include x-ray fluorescence, inferred microscopy, neutron activation, mass spectroscopy, and electron microscopy. The ability to analyze small amounts of material, yet obtain a sufficiently wide range of target compounds, is important for the routine use of the instrumentation. (RPIS 10306)

University of Maryland

College Park, MD 20742

Department of Meteorology

806. Intercomparison of Radiation Codes in Climate Models Phase II: Verification and Calibration

R.G. Ellingson

(301) 405-5386

\$427,000

The ICRCCM found large differences—30 to 70 $W \cdot m^{-2}$ —among fluxes predicted by sophisticated radiation models for identical atmospheres. The differences are partly due to the lack of an accepted theory for spectral line shape and continuum absorption. However, it is impossible to sort out these and other intermodel differences because of the lack of a set of accurate atmospheric spectral radiation data measured simultaneously with the important radiative properties of the atmosphere. The object of this research is to carry out a comprehensive program of measurement and analysis called Spectral Radiance Experiment (SPECTRE). SPECTRE establishes an absolute standard

for comparing models and aims to remove the "hidden variables" (unknown humidities, aerosols, etc.) invoked by radiation modelers to excuse disagreements with observation. This program should lead to more accurate radiation models for use in parameterizing climate models, which, in turn, play a key role in the prediction of CO₂/tracegas greenhouse effects. The major part of SPECTRE consists of two surface spectrometer teams and the Radio Acoustic Sounding System (RASS) for temperature profiling. Many other instruments, such as lidars, are available at no extra cost to SPECTRE because SPECTRE is designed as a subprogram of the FIRE Cirrus II project. Small changes in cirrus are capable of exerting large positive or negative feedbacks on trace gas greenhouse climate changes. By coordinating with FIRE, SPECTRE has a unique opportunity to contribute not only to the understanding and modeling of trace gas greenhouse effects but also to the cirrus greenhouse effect. A major ICRCCM goal is to evaluate the ability of radiation codes used in climate models to simulate the real atmosphere. SPECTRE contributes to achieving this goal by providing observations for comparison with model projections. The observations and analyses are critical to improving the ability to predict global change and link the multiple processes from increased greenhouse gases to the observed climate changes. (RPIS 10235)

University of Miami

Miami, FL 33149

Rosenstiel School of Marine and Atmospheric Sciences

807. Use of a Laser-Based Monitoring Technique to Measure Trace Gas Fluxes Across the Air-Sea Interface

R.G. Zika

(305) 361-4715

\$57,000

The objectives of this research are (1) to develop a sensitive, photothermally based spectroscopic technique for measuring the in situ weak infrared absorption of atmospheric carbon gases and (2) to initially assess its use in two important areas of air-sea transfer. The research provides improved measurements and quantification of the fluxes of trace and carbon gases at the atmospheric chemistry and the ocean CO₂ flux and trace gases. It develops improved measurement techniques which should improve scientific understanding. For many trace gases of interest (e.g., CO₂, CO, CH₄ and nonmethane hydrocarbons), the magnitude and even the sign of the air-sea concentration difference, which is the term driving the gas flux across the air-sea interface, are poorly known. The variability of this concentration difference has only recently begun to be addressed on the spatial and temporal scales appropriate to oceanography. Consequently, calculation of global fluxes of these crucial atmospheric components is constrained. Many observations must be made to provide reliable, globally averaged values for these terms and analytical methodologies must be developed which overcome the technical difficulties of many of the measurements.

The two areas of air-sea transfer studied are (1) abiotic photochemical production of atmospheric trace gases in the surface ocean and (2) photoperiod control of biologically respired trace gases in the surface ocean. The instrumentation development produces a sensitive technique for measuring atmospheric carbon and trace gases at the atmosphere-ocean interface, using photothermal deflection spectroscopy (PDS) that utilizes a pump laser beam. This is directed at resolving scientific issues related to disagreements between current measurement and modeling techniques. The PDS method can be very sensitive and provide a fast response gas sensor. Both capabilities are critical to the quantification of carbon and trace gases at the atmosphere-ocean interface. (RPIS 10311)

National Aeronautics and Space Administration

New York, NY 10025

Goddard Institute for Space Studies

808. Observational Analysis of Climate Feedbacks and Trends

A.D. Del Genio

(212) 678-5500

\$147,000

The objectives of this project work are to reduce the uncertainty in global climate sensitivity analyzing observations of currently unconstrained feedback processes and to define useful climate parameters and regions for detecting greenhouse gas-induced climate changes in the 1990s. Past attempts to compare model predictions of response to trace-gas trends have been inconclusive. If successful, the techniques applied under this research will constrain climate models, reducing uncertainty in linking increasing trace gases to climate change. The research analyzes global observations of several climate parameters central to the detection and understanding of long-term climate change due to an increasing greenhouse effect. This study focuses on three parameters that act as important but poorly understood feedbacks or forcings for climate change: clouds, water vapor, and ozone. The International Satellite Cloud Climatology Project and stratospheric aerosol and gas experiment I and II data sets are the primary sources of information on these variables, supplemented by available data from scanning multichannel microwave radiometers. First, these data sets are being searched for evidence of correlated variations on seasonal or interannual time scales, which reveal the sense of climate feedbacks, especially those produced by changes in moist convection strength or depth. By the third year of the project, each of the data sets will span almost a decade. It may then be feasible to seek long-term trends and correlated patterns of change in the data as evidence of an increasing greenhouse effect. Because clouds, water vapor, and ozone all have the potential to affect upper troposphere or lower stratosphere temperatures, the research will assess whether any changes observed are consistent with radiosonde evidence of long-term trends in the vertical thermal structure of the atmosphere. (RPIS 10236)

**National Aeronautics and Space
Administration**
Greenbelt, MD 20771

Goddard Space Flight Center

**809. Cirrus and Aerosol Profillometer for Radiometric
Measurements**

J. Spinhirne

(301) 286-9099

\$60,000

A micropulse LIDAR (MPL) is used to develop a small, eye-safe, autonomous laser remote-sensing system with sufficient sensitivity for detecting and profiling cirrus clouds. The project demonstrates a prototype MPL suitable for sustained, unattended ceilometry measurements of cirrus clouds at an Atmospheric Radiation Measurement (ARM) program Cloud and Radiation Testbed (CART) site. A prototype MPL is assembled which implements a high pulse-rate (10 KHz) diode-pumped Nd:YLF laser source and a germanium Geiger-mode avalanche photodiode detector. The prototype MPL uses a 0.2 nm-width spectral filter and a 0.1 milliradian field-of-view to limit interference of solar background. Photon-counting detection methods are incorporated in the MPL system. Data acquisition, averaging, and storage are performed by a PC-compatible computer with a single-card photon counting system. The initial MPL system is demonstrated in cooperation with Pennsylvania State University at the ARM-sponsored Pilot Radiation Observation Experiment (PROBE) in the Tropical Western Pacific during fall and winter of 1992. Following PROBE, MPL demonstration and evaluation is conducted at the ARM Southern Great Plains CART site. (RPIS 10612)

**810. Theoretical Cloud Radiation Studies in Support of
the Atmospheric Radiation Measurements Program**

W.J. Wiscombe

(301) 286-8499

\$168,000

The researchers for this project are developing a three-dimensional radiation transfer model and making it available to the Atmospheric Radiation Measurement (ARM) program as a "community model." In the process of developing this model, researchers are learning a great deal about the statistical nature of clouds and about ways to represent clouds in models. The eventual product of this research will be a three-dimensional radiation transfer model. The first task is to develop models for the spatial distribution of cloud optical depths based on the fractal nature of clouds. These models are constrained by data from FIRE and Landsat and by principles from turbulence theory and cloud physics. As a test of their applicability, models are applied to cloud types that have not been used in the development phase. Thus, while the properties of stratocumulus clouds may be used to develop these models, model statistical accuracy is tested by comparison to cirrus clouds. The second task is to further develop the Goddard

one-dimensional Monte Carlo radiation model. This task involves both an attempt to reduce the computer time requirements for this model (by a variety of approaches) and the extension of this one-dimensional model to handle a two-dimensional checkerboard grid of cloud optical depths in space. With a two-dimensional field of optical depths, the model becomes a three-dimensional radiative transfer model that can treat cloud fields that are inhomogeneous in two dimensions. The third task is to further develop a three-dimensional Fourier transform radiation model as an alternative to the Monte Carlo model. The fourth task is to use the three-dimensional radiation model together with the cloud optical depth model from the first task to study the sensitivity of the bulk cloud optical properties (i.e., transmission and reflection) to the optical depth distribution. These studies are used to evaluate the adequacy of current assumptions that one-dimensional radiative transfer models can be used to treat the three-dimensional cloud field within each "pixel" (or grid box in a general circulation model). The fifth task is to document and generalize both three-dimensional radiative transfer models (i.e., those developed in the second and third tasks so as to be appropriate "community models" for ARM and Clouds and Radiation Testbed (CART) sites. The sixth task is to use the models developed in the first three tasks and the ARM data to test the extent to which averages of time-series data at a single point can be used to represent spatial averages. The seventh task is to study stochastic radiative transfer as a shortcut to using a brute-force method (wherein many realizations of different cloud geometries must be calculated) to gather reasonable statistics on cloud radiative properties. (RPIS 10362)

National Center for Atmospheric Research
Boulder, CO 80307

Cloud Climate Interaction Group

**811. A Hierarchical Approach to Improved Cloud-
Radiation Parameterizations for Climate Models
Through the Atmospheric Radiation Measurement
Program**

J.T. Kiehl

(303) 497-1387

\$301,000

The project seeks to improve the parameterization or representation of radiation algorithms in general circulation models (GCMs) with respect to the impact of convective clouds and the range of mass fluxes to be expected. The products of the research are improved representations and parameterizations for the National Center for Atmospheric Research (NCAR) Community Climate Model (CCM) and the Geophysical Fluid Dynamics Laboratory (GFDL) GCM for the formation and radiative impact of convective clouds. Initially, the effectiveness of CCM and GFDL climate model radiation modules is tested using Atmospheric Radiation Measurement (ARM) observational data. Subsequently, the resolved convection model is evaluated for use in accounting for deep convective

clouds explicitly. The effects of deep convection on the thermal and atmospheric structure of the atmosphere, as well as the radiative effects of the clouds, are examined and compared to observations. Using observational data for validation, the effects of radiative interactions on cloud lifecycle are examined and the appropriate terms in the mass flux cloud parameterization in the NCAR CCM defined. Improved algorithms are implemented in CCM and GFDL GCMs. (RPIS 10619)

Mesoscale and Microscale Meteorology

812. Development and Testing of Parameterizations for Continental and Tropical Ice Cloud Microphysical and Radiative Properties in General Circulation and Mesoscale Models

A.J. Heymsfield

(303) 497-8943

\$137,000

New understanding of the radiative properties of clouds in the middle and upper atmospheres, especially those containing ice, helps develop and test parameterizations for use in general circulation models (GCMs). New parameterizations address the impact of ice or ice-water clouds on the atmospheric radiation balance as it is represented in GCMs. Data from Fire, Tropical Ocean-Global Atmospheric, and Atmospheric Radiation Measurement programs on the microphysical characteristics of altocumulus clouds and dense cirrus are used with measurements of the bulk radiative impact of these clouds to develop new parameterization concepts. Measurements of ice particle size spectra, crystal shapes, and ice-water content are made using in situ measurement techniques, e.g., balloon-borne instruments and aircraft, and are correlated to ground-based radar and lidar signals. Relationships determined are represented in parameterizations of cloud radiative properties in terms of cloud microphysical properties. Parameterizations are implemented in several GCMs and subjected to sensitivity analysis studies to understand the impact of these clouds on GCM performance. (RPIS 10621)

Wave Propagation Laboratory/ERL

813. Shipboard Measurements of the Cloud-Capped Marine Boundary Layer During Fire/Atlantic Stratocumulus Transition Experiment

R.A. Kropfli

(303) 497-6235

\$292,000

The research explores issues relevant to the establishment of an oceanic Atmospheric Radiation Measurement (ARM) Program Cloud and Radiation Testbed (CART) site and obtains an unprecedented data set on marine clouds and radiation. Technical papers are published that are useful for identifying technical and logistical issues associated with establishment of an ARM Program ocean-based CART site. An existing suite of National Oceanic and Atmospheric Administration (NOAA) Wave Propagation Laboratory (WPL) surface-based remote sensors are deployed on a ship during the Atlantic

Stratocumulus Transition Experiment (ASTEX). The instrument suite includes a Doppler lidar, a Doppler cloud radar, a Doppler wind profiler, a water vapor/liquid microwave radiometer, and a Radio Acoustic Sounding System. These systems are deployed on an oceanographic and meteorological research ship and on shore. Measurements are compared with those acquired using similar island-based sensors operated by Pennsylvania State University, Colorado State University, and NOAA WPL. (RPIS 10610)

New York University

New York, NY 10003

Department of Applied Science

814. Cloud and Ocean Effects on Greenhouse Warming

M.I. Hoffert

(212) 998-8995

\$228,000

The project objectives are to (1) investigate effects of global cloudiness variations on global climate and their implications for cloud feedback and (2) continue development and application of New York University transient climate/ocean models, with emphasis on coupled effects of greenhouse warming and feedbacks by both the clouds and oceans. The research provides a quantitative assessment of how transient climate change may be hidden by cloud feedbacks and ocean thermal delay. It emphasizes the use of cloud, surface temperature, and ocean data sets as interpreted by a focused climate/ocean model (1) to develop a cloud radiative forcing scenario for the past 100 years and to assess the transient climate response, (2) to narrow key uncertainties in the system, and (3) to identify those aspects of the climate system most likely to be affected by greenhouse warming over short, medium, and long time scales. Apart from short-term transients on the decadal time scale, the research approach aims at better understanding of latent climatic effects, i.e., global climatic and environmental changes to which the planet may be effectively committed, but which are temporarily hidden as a result of thermal storage by the oceans. Effects of cloud radiative forcing on global climate response are assessed using an extension of the methodology Prof. Hoffert and colleagues previously employed to assess solar variability effects on climate. The simplified model used this way assists in developing an understanding of the key processes before investigating with the general circulation models. (RPIS 10305)

Science Applications International Corp.
San Diego, CA 92121
815. Evaluation of a New General Circulation Model-Capable Stochastic Cloud/Radiation Parameterization Using Atmospheric Radiation Measurement Data
R.N. Byrne
(619) 546-6485
\$174,000

Atmospheric Radiation Measurement (ARM) cloud morphology and cloud/radiative energy balance data are used to define the parameters for a new cloud parameterization technique based on an innovative stochastic radiative transfer technique. The project is developing a validated stochastic cloud/radiation transfer parameterization for use in general circulation models (GCMs). Stochastic radiative transfer techniques are adapted from nuclear physics for application to radiative transfer in the presence of clouds. Clouds and clear air are treated as a two-component stochastic system wherein subgrid radiative transfer through partial cloud cover is a natural consequence. Algorithms developed are evaluated using ARM and satellite data in the Scripps single-column semiprognostic model and used to explore the accuracy required to achieve a specified level of accuracy for atmospheric energy deposition by radiative processes. GCM sensitivity studies are conducted using National Center for Atmospheric Research Community Climate Model. (RPIS 10609)

Scripps Institution of Oceanography
La Jolla, CA 92093
Space Institute
816. Atmospheric Radiation Measurement Tropical Pacific Experiment: Role of Cloud, Water Vapor and Convection Feedbacks in the Coupled Ocean/Atmosphere System
V. Ramanathan
T. Barnett
(619) 534-6381
\$662,000

The objectives of this research are to observe and model the radiative feedbacks and energy fluxes in the tropical western Pacific and to use this understanding to advance climate model development. The product will be an increased understanding of the enhanced greenhouse effect and the role of clouds in modifying the effect. A two task approach is used to mesh with the Atmospheric Radiation Measurement (ARM) Program and the Computer Hardware, Advanced Mathematics, and Model Physics program. Task 1 develops the data processing and imaging techniques to combine ARM data with satellite data. The work is closely coordinated with the ARM science team to assure that the satellite data and the ARM data complement each other, as well as provide the data essential for testing the

hypothesis of the super greenhouse effect in the tropical western Pacific. The satellite data include atmospheric profiles of temperature and humidity, estimates of total water vapor, and three-dimensional radiative information for cloud research. Task 2 uses a coupled ocean/atmosphere general circulation model (GCM) to seek understanding of the measurements and to assist in selecting the elements to be measured. The model is used to assist in validating and advancing the cloud-radiation parameterizations used in GCMs, with emphasis on the role of tropical convection. The seasonal cycle and the El Niño/Southern Oscillation data (including the satellite data) are used in conjunction with the model. The hypothesis is that a "super" greenhouse must be induced by the unique energy balance, with the clouds regulating the sea surface temperature, yet owing their existence to the warm SSTs and convection. State-of-the-art, three-dimensional visualization is used in both tasks to aid in understanding of the separate products of each task and in the comparison of data and model information. (RPIS 10517)

Southern Methodist University
Dallas, TX 75275
Department of Statistical Sciences
817. Statistical Examination of Climatological Data Relevant to Global Temperature Variations
W. Woodward
H. Gray
R. Gunst
(214) 692-2457
\$202,000

The objective of the research is to construct a state-of-the-art statistical model of global temperatures. Statistical analysis of the available data leads to better identification and understanding of the variables and the changes in the variables that are associated with the predicted CO₂-induced climate change. This research develops a model for measures of mean global temperature using state-of-the-art statistical techniques, appropriate new methodology, and a variety of databases consisting of relevant explanatory variables. This effort includes developing a definition of CO₂-induced climate change. Attention is given to ensuring the integrity of the data. The hypothesis of a recent warming trend is tested, and the impact on warming of changes in the explanatory variables is investigated. The contribution of each of the explanatory variable to the cycles, trends, and random variations in the warming/cooling process is ascertained. Data sources include not only recent records but also biological and chemical data collected from archeological and geological studies. A statistical model is constructed relating global temperature to a collection of explanatory variables. Development and use of appropriate transfer function models, including the possibility of long-memory processes, is a major thrust of the research. (RPIS 10312)

State University of New York, Albany

Albany, NY 12205

Atmospheric Sciences Research Center

818. Use of Cloud Observations and Mesoscale Meteorology Models To Evaluate and Improve Cloud Parameterizations

C.J. Walcek

(518) 442-3840

\$79,000

The three project objectives are to (1) identify relationships between fractional cloud coverage and various meteorological parameters using satellite cloud coverage data sets and a known mesoscale meteorological model; (2) determine the radiative and dynamic impact of fractional cloud coverage; and (3) parameterize these relationships and impacts. Improved cloud coverage parameterization techniques are being developed for use in general circulation models. High resolution output from a mesoscale meteorological model and digitized satellite cloud coverage data are analyzed and correlated. Larger scale meteorological parameters that correlate well with cloud cover are identified and quantitatively defined; these may include coupled relationships that involve several meteorological parameters, such as relative humidity and stability. Various time and space scales are examined to extend the mesoscale analyses to larger scale model applications. A comprehensive mesoscale model is developed and used to assess the interaction of cloud-scale processes with the larger scale meteorological environment. Model performance in reproducing larger scale meteorological processes from this approach is evaluated against earlier models in which cloud cover data were used. (RPIS 10608)

Syracuse University

Syracuse, NY 13244

Department of Geology

819. Mechanisms Controlling the Production and Transport of Methane, Carbon Dioxide, and Dissolved Solutes Within a Large Boreal Peat Basin

D.I. Siegel

(315) 443-2672

\$159,000

The project objectives are to determine the degree to which solute and gas movement in deep organic soils is controlled by (1) local groundwater flow systems and their associated vegetation community types and (2) regional subsurface hydrogeologic settings. The research assists in defining the potential release of CO₂ and methane from boreal peat basins. Peatlands are an important carbon storage reservoir, but little is known about their dynamics and potential feedbacks. This is because they are sensitive to change, and the changes have the potential to significantly alter the carbon storage release balance. The project uses an integrated modeling and field study of solute transport and groundwater flow conditions in

the Glacial Lake Agassiz Peatlands of northern Minnesota to investigate: (1) rates of carbon accumulation and loss, as well as fluxes of methane and CO₂; (2) the physical and botanical factors controlling the production of methane and CO₂ within the peat profiles; and (3) the role of hydrogeological processes in controlling the fluxes of gas solutes through the peat. Measurements are taken of hydraulic head gradients and solute/gas concentrations in the major vegetation communities of the peatland. The fluxes of dissolved solutes and gases from the peat in each vegetation setting are determined from these data by mathematical modeling of the advection-dispersion equation, tested by isotopic mass balances on carbon. Results from these detailed site-specific studies are integrated into the larger peatland setting by relating the variations in solute fluxes to the proportions of each major vegetation type in the larger peatland. The chemical portion of this study relies on microsampling of gases and solutes obtained throughout the depth profile of the peat. Standard methodologies are applied. Isotopic analysis (DELTA C-13) is used to provide evidence for the processes by which methane is produced and transformed within the peat. (RPIS 10308)

Texas A&M University

College Station, TX 77843

Climate System Research Program

820. Signal and Noise in Global Warming Detection

G.R. North

(409) 845-8083

\$101,000

The objective of this project is to estimate the length of climatological record required to identify a global warming signal over natural variability. The product of the research is an understanding of the adequacy of the historical instrument record to resolve the issues of signal and noise in documenting global warming.

The scientific debate as to whether or not the climate has changed—and the cause of any change—hinges on the historical data set. If the record is not sufficient to resolve natural variability over the period of observation (e.g., signal to noise), then the possibility of a quantitative link is slim.

The research increases understanding of the global trend-observing system by statistical analysis of the variability about trends into their natural and random sampling components. The researchers use idealized mathematical models such as noise-forced energy balance models and global climate model (GCM) runs of idealized planets to produce long time-series data for analysis. This procedure provides the long record required to assess how long a data set may be required to determine natural variability. Although these are not "real" data, they must be understood before more complicated climate models are applied.

The researchers use a formalism recently devised for sampling error analysis. The technique is applied to a physical field exhibiting random fluctuations over a space-time spectrum. For this research, the technique is applied to the

space-time spectrum of the surface temperature field. The first year's effort concentrates on analyzing the output of a sample energy balance model. The second year's effort expands the analysis to include a simplified version of the National Center for Atmospheric Research GCM. Research in the third year is governed by the results of the first two years' analysis. (RPIS 10310)

University of Wisconsin, Madison
Madison, WI 53706

Cooperative Institute for Meteorological Satellite Studies

821. Atmospheric Radiation Measurement Fourier Transform Spectrometer Data Analysis Tools

W.L. Smith

(608) 262-0544

\$191,000

Radiative transfer models are developed and tested through the analysis of the spectral radiance and solar absorption data collected at the Atmospheric Radiation Measurement sites. Data analysis tools are specifically tailored to retrieve various atmospheric parameters including cloud optical properties, and temperature and moisture profiles from observational data from the Atmospheric Emitted Radiance Interferometer (AERI), Atmospheric Emitted Radiance Interferometer, and Solar Radiance Transmission Interferometer (SORTI) Fourier Transform Infrared (FTIR) instruments. This effort develops and tests radiative transfer algorithms to derive atmospheric state parameters from FTIR observations. Through the comparison of theoretical calculations, using FASCODE, the HITRAN database, and FTIR observations, the research team develops techniques for inferring atmospheric temperature and moisture profiles, trace gas information, and cloud radiative properties from data acquired with AERI, AERI-X, and SORTI instruments. (RPIS 10606)

Department of Meteorology

822. Parameterization of General Circulation Model Subgrid Nonprecipitating Cumulus and Stratocumulus Clouds Using Stochastic/Phenomenological Methods

R.B. Stull

(608) 262-9862

\$66,000

The project investigates the use of statistical distributions of boundary-layer characteristics to describe and parameterize the phenomenological evolution of cumulus and stratocumulus clouds. The product is a one-dimensional boundary layer and subgrid cloud parameterization for incorporation into general circulation model one-dimensional models. This effort involves a mix of deterministic and statistical models focused on providing parameterizations of boundary layer clouds for GCMs. The statistical processes are useable with models other than the one-dimensional general measurement strategy to be

used in the Atmospheric Radiation Measurement program. Using data from previous field programs, the statistical distribution of boundary-layer turbulence and depth, as a function of stability and moisture, is determined and parameterizations are developed. Examples include surface heating and evaporation parameterizations based on the surface radiation budget, shading by individual clouds, and land-use patterns. Boundary-layer depth parameterizations include convergence/divergence in the boundary layer. Statistical cloud fields produced by the boundary-layer parameterizations are allowed to feedback into the evolution of the model boundary layer. (RPIS 10605)

Global Change: Carbon Cycle and Vegetation Research

Intramural DOE Laboratories

Brookhaven National Laboratory
Upton, NY 11973

Terrestrial and Aquatic Ecology

823. Free Air Carbon Dioxide Field Enrichment Facility Development

G. Hendrey

(516) 282-3262

\$935,000

There are three principal objectives for this project: (1) to develop and test a free-air gas delivery system for enriching a field crop to specified levels of CO_2 ; (2) to characterize physical and biological conditions of the Maricopa Arizona field site prior to field experiments with cotton at specified levels of CO_2 ; and (3) to obtain physiology, growth, and yield data for validating a plant simulation model, COTCO₂. The products are twofold: (1) an experimental facility for maintaining specified levels of CO_2 in the canopy of a cotton crop throughout an entire growing season and (2) a field data set on plant response to CO_2 enrichment. A monoculture of cotton is a representative stand of plants for testing system performance, and the research is carried out in cooperation with Agricultural Research Service modeling and experimental research groups. Once performance is tested, the system is deployed with various vegetation types and natural systems. Realistic field data on the effects of increasing ambient CO_2 concentrations on the flux of carbon between the biosphere and atmosphere are obtained from a CO_2 enrichment experiment in an agricultural field. Concentrations of CO_2 are controlled in a free-air setting by regulating the mass flow of pure CO_2 into a 22-m diameter dispersion system. The CO_2 is prediluted by mixing with ambient air prior to release through 32 independently valved vertical vent pipes (VVP). Opening of VVPs is controlled by wind direction. The mass of

CO₂ released is proportional to wind velocity, but is also adjusted by feedback regulation based on 1-sec measurements of CO₂ in the center of the array. Free Air Carbon Dioxide Field Enrichment (FACE) CO₂ delivery/control systems are being constructed for use in joint research with the U.S. Department of Agriculture to produce validation data for evaluating CO₂ effects with native and agricultural species/vegetation. The field experiment is producing biological data on physiology, growth, and plant/environment interactions for ambient and elevated CO₂ treatments and for irrigated and water stress conditions. (RPIS 4827)

Oak Ridge Institute for Science and Education

Oak Ridge, TN 37831

Science/Engineering Education Division

824. Postdoctoral Research Program for Global Change

L. Holmes

(615) 576-3192

\$2,310,000

This project is designed to increase the involvement of scientists and engineers in areas supporting all aspects of the Government's mission in global change research. To achieve this objective, the project enables recent doctoral degree recipients to conduct research on projects related to global change. Through continued postgraduate education, the project provides a flow of scientists and engineers into DOE and other laboratories to support current and long range research needs. Appointments of up to 2 years can be made at laboratories with research programs supporting global change projects. Participants collaborate on a full-time basis with professionals working on Government-supported or related projects, have access to onsite resources and facilities, and become familiar with the Government global change research initiative. (RPIS 5476)

Oak Ridge National Laboratory

Oak Ridge, TN 37831

Environmental Sciences Division

825. Carbon Dioxide Information Analysis Center

R. Cushman

(615) 514-0390

\$2,050,000

The objectives of this project are to acquire or compile, quality assure, document, archive, and distribute CO₂-related information in support of DOE's Carbon Dioxide Research Program (CDRP). The project provides the fully integrated information analysis center needed to support CDRP and to provide CO₂-related information to the research and policymaking communities. The Carbon Dioxide Information Analysis Center (CDIAC) identifies users' needs by working closely with the research community, CDRP, and policymakers by attending workshops, reviewing the literature, and maintaining personal contacts. Data, models, and other products and services are evaluated for usefulness and

acquired, if available, or compiled at CDIAC if not in a usable form. These products undergo extensive quality assurance and complete documentation in full coordination with the original supplier of the information. They are then made available to the research and policymaking communities. The Center works with other data centers and individual researchers to promote the compilation and exchange of data. The Center's activities and approaches are evolving with changing research needs and technology. Emphasis is being placed on using new methods of communication (electronic bulletin boards), new media for archiving and distribution (compact disc read-only memory), and new data products (geographic information systems and fully registered and projected cartographic data packages). These new approaches to information management complement the suite of CDIAC tools. The Center's research activities reflect new CDRP programmatic directions. Activities include information support for the evaluation of complex environmental issues associated with elevated levels of atmospheric CO₂, including the technical management aspects of the national CO₂ program. (RPIS 3939)

826. Carbon Dioxide Information and Analysis Research Program: Resource Analysis

R. Cushman

(615) 574-0390

\$50,000

The objective of this project is to plan, monitor, and produce data sets needed for analyses that project the consequences of changing CO₂ and climate on natural and societal resources. This project is producing two principal products: (1) evaluations of current issues concerning the responses of natural and societal resources to changing CO₂ and climate, including responses to climate-induced rising sea level, and (2) assembly of data bases useful for analyses of the responses of resources to changing CO₂ and climate. Current issues concerning the responses of resources to changing CO₂ and climate are analyzed based on critical reviews of the literature. Methods for analyzing the response of resources to changing CO₂ and climate are being investigated, including the definition of regions for use in regional resource analyses and the application of climate model output in resource analyses. A global coastal hazards database based on geology, geomorphology, terrain, tidal range, wave heights, trends in relative sea level, and other variables is being further developed to identify those coastal areas that are especially susceptible to erosion and inundation. Other data bases are being developed as needed for specific resource analyses. Geographic information systems are being applied to the analyses of this subtask where appropriate. (RPIS 4990)

827. Carbon Cycle Program Management

W.R. Emanuel

(615) 574-0390

\$1,300,000

Task 1 of this project seeks to clarify the relationships between fossil-fuel emissions and atmospheric CO₂ concentration that control further CO₂ increases as fossil-fuel use continues. This task takes a total-carbon-cycle approach and integrates data,

concepts, and models from the atmospheric, terrestrial, and oceanic projects. The Carbon Dioxide Information Analysis Center produces annual updates of emissions estimates based largely on data compiled by the United Nations Statistics Office. It is producing models of the global carbon cycle and underlying data (including descriptions of carbon dynamics in the terrestrial and oceanic reservoirs) and analyses to clarify potential responses of atmospheric CO₂ to further fossil-fuel use. Task 2 focuses on developing a realistic model of carbon turnover in terrestrial ecosystems as it affects responses to fossil-fuel emissions. Task 2 is producing terrestrial carbon-cycle models and their underlying data sets. These are to be incorporated into the total global carbon cycle models described in Task 1, with land-use summaries provided for specific regions of interest. Task 3 aims to improve the representation of oceanic carbon cycling in models and to interpret new oceanic data in terms of changing atmospheric CO₂ concentration. Specifically, it is determining the biological processes that must, at a minimum, be explicitly considered in the analysis of changes in atmospheric CO₂ levels and incorporating a representation of these processes into the reference models. This activity provides an avenue for bringing results from DOE's oceans program into the development of total-carbon-cycle models. Altogether, the task yields refinements to oceanic carbon-cycle models and analyses of ocean data in terms of the influence of the oceans on atmospheric CO₂ responses to fossil-fuel emissions. (RPIS 4181)

828. Elevated Carbon Dioxide Effects on Woody Plant Soil Systems

L. Norby

(615) 574-7301

\$400,000

There are three objectives for this project: (1) to determine whether temperate forest trees increase in growth and carbon storage as the concentration of carbon dioxide in the atmosphere increases; (2) to investigate mechanisms of nutrient cycling in relation to tree-growth change as influenced by atmospheric CO₂ concentration; and (3) to compare simulated tree ring chronologies with field data on forest response to CO₂ increases and to develop methods for scaling up soil-plant models in space and time. The tasks include conducting controlled-environment experiments, assembling a field facility for CO₂ enrichment in open-top chambers, observing growth and physiological responses under field conditions, observing nitrogen cycling, detecting historical CO₂ and climate effects, and scaling up soil-plant models in space and time. (RPIS 3457)

Pacific Northwest Laboratory

Washington, DC 20024

829. Energy and Future Carbon Dioxide Emissions

J.A. Edmonds

(202) 646-5243

\$328,000

There are three major objectives for this project: to develop the scientific basis to make and bound projections of future energy-related emissions to the atmosphere of carbon dioxide and other radiatively important gases; to support DOE in its participation in the Intergovernmental Panel on Climate Change (IPCC); and to support DOE in its participation in the Committee on Earth Sciences. This project will provide results in five major areas: IPCC support; model development; database development; U.S./Japan energy/gross national product (GNP) comparison; and energy and methane. In the field of IPCC support this project supports DOE in its participation in the IPCC, Response Strategies Working Group (RSWG), Energy and Industry Subgroup (EIS). In terms of model development this project is geared toward development of the theoretical structure for a revised energy-economic model of CO₂ and other radiative precursor emissions and toward the initial development of model codes. In the area of database development, this project is producing a completed global disaggregated energy production and use database for the years 1975, 1980, and 1983 that is consistent with the revised long-term global energy-economic model. This work is coordinated with the Brookhaven National Laboratory and the Oak Ridge National Laboratory and completes work begun on the development of this database in FY 1987. An analysis of the observed differences in aggregate energy intensity between the U.S. and Japan is also being produced for a U.S./Japan energy/GNP comparison. In the area of energy and methane, this project includes examination of the relationship between energy production and use and the release of methane to the atmosphere. This project completes work begun in FY 1988. (RPIS 4843)

830. Resource Analysis Research*J. Edmonds**M. Scott**(202) 646-5243***\$55,000**

This project seeks to develop the scientific information base and analytic tools needed to describe the nature/kind, timing, magnitude, and uncertainty associated with the consequences of increasing atmospheric CO₂ and climate change on human and natural systems. This effort includes describing direct and indirect effects (e.g. water resources interactions with the energy system) at the regional level and the interactions among regional system changes and responses within and between regions.

Program coordination involves coordinating proposals requested, received, and evaluated for the Resources Analysis Research Project (previously called Precursor to a Methodology Project). It also involves coordinating the Regional Analysis and Knowledge Transfer areas to insure that efforts at all program levels are focused on the goals of the overall project and the Resources Analysis Area. The selection of a region for analysis.

Regional analysis involves developing a research plan for the methodology development and designing and developing a baseline description of the resources and interactions within the region for today's climate and resources. It also involves analysis of the impact of a historical analogue climate with today's resources, and a future climate scenario with resources that can be expected to prevail early in the 21st century.

Knowledge transfer involves identifying the most important research issues to be addressed by the Resources Analysis Research Project and the transferring of knowledge needed by the project from outside the DOE/CDRD Resources Analysis Research Project to the project. In FY 1990, this area transferred knowledge gained in the conduct of the Resources Analysis Research Project to those who are potential beneficiaries of that knowledge via one domestic workshop. This area will secure peer review of the knowledge gained in the project via appropriate reviews. (RPIS 5128)

Global Change: Carbon Cycle and Vegetation Research

Offsite Grants

**U.S. Department of Agriculture—
Agricultural Research Service**
 Beltsville, MD 20705

Agricultural Systems Research Institute**831. Simulation Modeling of Crop Response to CO₂ Enrichment***B. Acock**(601) 323-2230***\$40,000**

This research has three main objectives: (1) to define a "generic" modular structure for models of plant growth and then develop and test modules needed as components of modular crop models, (2) to perform sensitivity/uncertainty analysis of the soybean crop model GLYCIM, and (3) to exercise the models in studies of the combined effects of CO₂ and temperature on plant growth. A validated, mechanistically based plant growth simulation model that can treat CO₂-dependent physiological processes of the whole plant and the associated environmental factors affecting growth is being produced.

The research for this project involves four main approaches:

(1) The "generic" approach incorporates essential CO₂-dependent processes and interactions, as well as physiology and growth processes common to many plant species. Modular concepts are employed in this phase of research. Researchers are also exploring ways to aggregate plant processes to represent generic functions using analytical approaches described for large area forecasts.

(2) The two-dimensional soil model, SOILSIM, treats movement of water and solutes in both the unsaturated (rooted) and saturated portions of the soil. The SOILSIM model is being incorporated into GLYCIM and is being validated by using data sets collected from all over the U.S.

(3) Sensitivity/uncertainty analysis of the soybean GLYCIM model continues. Because this model is the most thoroughly tested of all physiologically based plant models, aggregate predictions attempt to account for production over wide areas. The models attempt to link to the lower boundary of the general circulation models, with initial attention to partitioning of energy at the surface. Albedo and stomatal conductance are the initial processes being examined.

(4) Refinement of plant model controls on carbon fixation and utilization in growth are being completed for COTCO₂, a state-of-the-art plant growth model developed jointly by DOE and the U.S. Department of Agriculture's Agricultural Research Service. Data from other CO₂ temperature experiments with wheat are being adapted to existing wheat models, and a new model is being developed for rice. (RPIS 9916(A))

**U.S. Department of Agriculture—
Agricultural Research Service
Gainesville, FL 32611**

**Plant Science Research Laboratories—University of Florida,
Agronomy Department**

**832. Assessment of Crop Response to Increased
Atmospheric Carbon Dioxide: Rising CO₂
Effects on Rice**

L.H. Allen

(904) 392-6180

\$150,000

The main objectives of this project are (1) to determine the direct effects of CO₂ and the interactive effects of temperature, water management, and nutrition on rice photosynthesis, growth, water use, and yield; and (2) to develop and/or adapt process-level crop model(s) for prediction of rice growth and yield responses to elevated CO₂ and to environmental and germplasm variables. Primary information is being produced on the physiology, growth, and yield of rice in relation to increasing atmospheric CO₂. The physiology and growth data are used in a simulation model of how interactions of CO₂ enrichment, variable temperature, and nutrient and water stress affect rice growth and productivity in a higher CO₂ world with different climate regimes.

The Plant Stress and Protection Research Unit is conducting a long-term study on the effects of increased atmospheric carbon dioxide on physiology, growth, and yield of rice at both optimal and stress levels of temperature, water, and nutrients.

The experiments derive response functions to CO₂ concentration under conditions of nonlimiting water and nutrients and near optimum temperatures. These results are used to determine coefficients for specific rate equations in order to modify and adapt an existing plant simulation model.

The combined temperature-CO₂ effects are being examined for several new cultivars obtained from the International Rice Research Institute. Ancillary measurements of CH₄ emissions in relation to varied environmental conditions (e.g., temperature, nutrient status) and physiological status help researchers identify biophysical controls on release from paddy rice. Companion experiments investigate interactive effects of CO₂ and nitrogen fertilization. An independent model validation experiment is also underway. (RPIS 9916(B))

**U.S. Department of Agriculture—
Agricultural Research Service
Phoenix, AZ 85040**

Water Conservation Laboratory

**833. Elevated CO₂: Modeling Cotton Response
Interactions with Temperature on Photosynthesis,
Insect Population Dynamics and Temperature
Interactions and Long-term Effects on Trees**

B. Kimball

(602) 379-4356

\$110,000

This research project has four main objectives: (1) to assemble data for use in modifying a plant growth simulation model that incorporates CO₂ and other climate variable effects into physiological processes affecting plant growth; (2) to determine the effects of elevated CO₂ on the growth and physiology of trees (*Citrus aurantium* L.); (3) to determine the effects of environmental factors, particularly CO₂ and elevated temperature, on "feedback inhibition" of photosynthesis and on rates of development and growth of plants organs; and (4) to determine the effects of temperature on growth, development time, and survival on beet armyworm and pink bollworm reared on plants grown at elevated CO₂ and to determine if these insects are affected by CO₂-altered tissue of plants.

The main product of the research effort is primary information on physiology, growth, and yield of plants, trees, and annual species in relation to increasing atmospheric CO₂. The physiology and growth data are used to improve equations of the simulation model, COTCO₂; and yield information represents validation data sets for testing the model. Controlled environment experiments produce data on the interactive effects of CO₂ and temperature on "feedback inhibition" of photosynthesis and enhancement of growth at higher temperature.

Taking advantage of full sunlight conditions at Phoenix, AZ, and using temperature-CO₂-controlled greenhouses, investigators have designed cotton studies to include two temperatures and two CO₂ concentrations. Switching experiments allows investigators to examine occurrence of "feedback inhibition" during photosynthesis, the sometimes observed phenomenon wherein supply of assimilates (related to elevated CO₂ and increased carbon fixation) may exceed demand, thus causing a decrease in photosynthetic capacity. When inhibition is observed, additional measurements are made to investigate intercellular phosphate and O₂ insensitivity of rubisco.

The open-top CO₂-enrichment chamber technique is used with ambient and 650-ppm levels of CO₂; plant physiology and growth are determined for different temperature conditions. An experiment with citrus continues to provide data on the CO₂ effects on leaf area, biomass, yield, foliage temperatures, net photosynthesis, stomatal conductance, photosynthetic response to CO₂, leaf carbohydrate content, and stomatal response at variable soil moisture content.

Carbon dioxide enrichment changes biochemical properties of plant tissue, a change that influences feeding habits and rates of foraging insects. The cotton experiment is furnishing plant material for an ancillary experiment to determine how the growth of beet armyworm is affected in host cotton grown at two levels of CO₂ and two temperatures. (RPIS 9916(C))

University of Bern CH-3012 Bern, Switzerland

Physics Institute

834. Simulations of the Carbon Cycle in the Oceans

U. Siegenthaler

011-41-31-658611

\$77,000

The objective of this project is to help in the continued development of three-dimensional models of the oceanic carbon cycle for simulating the ocean's uptake of anthropogenic CO₂. Researchers are producing three-dimensional model simulations of anthropogenic CO₂ uptake; they are also determining the sensitivity of that uptake to various factors. In addition, simulations using a 1.5-dimensional model are being carried out. "Projection" of the three-dimensional model results onto the 1.5-dimensional model helps investigators to better understand the carbon cycle; this process also permits use of the simple model as an economic substitute for the three-dimensional model in calculating the response to arbitrary CO₂ emission scenarios.

The three-dimensional model runs are carried out at Princeton University. Investigators at the University of Bern help to plan and evaluate the model experiments based on their experience with simple carbon cycle models. Simple models that allow extensive sensitivity tests and comparison of different oceanic tracer fields are being developed and used. Circulation and tracer fields from the three-dimensional model are projected to one and two dimensions for deriving parameterized transport coefficients comparable to those used in simple models. (RPIS 10350)

University of California, Los Angeles, Laboratory of Biomedical and Environmental Sciences

Los Angeles, CA 90024

Environmental Sciences Division

835. CO₂ Exchange, Environmental Productivity Indices, and Productivity of Agave and Cacti Under Current and Elevated Atmospheric CO₂ Concentrations

P.S. Nobel

(213) 825-3395

\$125,000

Working with Crassulacean acid metabolism (CAM) plants, researchers have chosen the following objectives for this project: (1) to examine the influence of elevated CO₂ concentrations and accompanying environmental changes on net CO₂ uptake and

productivity; (2) to use the Environmental Productivity Index (EPI) to evaluate plant response to the CO₂ enrichment in relation to soil water status, air temperature, and photosynthetic photon flux density; and (3) to examine the molecular basis for interpreting CO₂ effects on CAM plant metabolism. Fundamental information is being produced on CO₂ fixation by the CAM pathway, which approaches the upper limit of CO₂ fixation by vascular plants.

Experiments with *Opuntia* allow researchers to investigate the dependence of CO₂ exchange on plant age; measurements of both transpiration and net CO₂ exchange help researchers determine water-use efficiency. The study is determining whether EPI holds for plants grown at elevated CO₂. The CO₂ enrichment experiments are conducted outdoors in open-top control chambers to take advantage of natural lighting and in situ conditions for growing plants.

Molecular studies will involve energy costs and molecular efficiency of the CO₂ fixation process at ambient and elevated CO₂ conditions. Fundamental energy requirements will be worked out for two different enzyme pathways, namely, ribulose-1, 5-bisphosphate (RuBisCO) and phosphoenol-pyruvate carboxylase (PEPCase) fix CO₂ and form carbohydrate molecules differently.

The metabolic pathways are being investigated by CO₂ gas exchange and by using carbon isotope fractionation, which is a more modern way to determine the relative importance of different pathways of carbon metabolism. Metabolites of the initial step of CO₂ fixation have different $\Delta^{13}\text{C}$ values that provide measures of relative enzyme intensity for different metabolic pathways, conditions, and time periods. (RPIS 10596)

Columbia University Palisades, NY 10964

Lamont-Doherty Geological Observatory

836. The Effects of Changing Land Use on Carbon and Nitrogen in Mid-Latitude North American Soil and Rice Paddies

W.S. Broecker

(914) 359-2900

\$58,000

The research seeks to determine how changing land use affects organic carbon storage in soil. The hypothesis is that much of the missing carbon in the global carbon budget resides in soils at depths not commonly measured in basic soil surveys. This project looks at time histories of carbon and nitrogen accumulation under anaerobic conditions of rice paddies. Burial and decomposition rates of rice chaff are reconstructed from sediment cores of different aged rice paddies. Carbon and nitrogen inventories of soil profiles are reconstructed in the corn belt and grasslands of central U.S., which have been subjected to different land uses. Carbon, nitrogen content, and radiocarbon and chemical characteristics are determined for soil humus. The study seeks "clues" regarding vertical penetration of chemically reactive species. Organic carbon and nitrogen fractions are measured for cultivated

soils and are compared with samples collected at undisturbed sites not affected by past agricultural practices. Carbon lost from upper soil layers and deposited in lower soil layers instead of being oxidized to carbon dioxide is measured. Also, measures of bulk soil density, porosity, moisture content, N/C ratios, C-14, Cs-137, and Pb-210 in soil fractions are used to identify processes of carbon storage in deeper soils as well as to estimate the residence time of various carbon fractions in soils. (RPIS 10587)

Duke University
Durham, NC 27706

Department of Botany

837. Modeling the Response of Plants and Ecosystems in CO₂ and Climate Change

J.F. Reynolds

(919) 684-2677

\$400,000

The objectives of plant modeling are (1) to construct generic models of leaf (GENLEAF), canopy (CANDO), and whole-plant (ALLOC) response to elevated CO₂ and climate change; and (2) to provide information to higher level models, such as community and ecosystem models.

The objectives of ecosystem modeling are (1) to incorporate models of plant responses to elevated CO₂ into a generic ecosystem model (SERECO) in order to predict the direct and indirect effects of elevated CO₂ and climate change on ecosystems; and (2) to use the ecosystem model to study effects of change in CO₂ and climate at regional and global scales. Ultimately, this study will involve linking to models of landscape dynamics and global carbon balance models.

Common objectives of both plant and ecosystem modeling are to: (1) validate model predictions of whole-plant and total ecosystem response against various field studies of elevated CO₂ and climate change; and (2) use these models to test specific hypotheses and to predict primary, secondary, and tertiary effects of elevated CO₂ and climate change on individual plants and on ecosystems for conditions and timeframes beyond those used to calibrate the model.

A suite of plant and ecosystem models analyzes the combined effects of CO₂ and changing climate conditions. After development and testing, the models are used to predict plant and ecosystem response to anticipated changes of the future physical environment (e.g., rising CO₂, warmer temperature, more or less moisture or light). As the most comprehensive, mechanistically based carbon dynamics model ever developed, SERECO will be applied to the question of carbon balance in terrestrial ecosystems.

The approach employs a suite of linked models. Refinement and testing of the GENLEAF module focuses priority attention on nitrogen, phosphorous controls on photosynthesis at high CO₂, carbon source/sink feedback effects on photosynthesis (particularly shifts in the A/C_i curves), and carbon metabolism of different plant tissues as influenced by elevated temperature. Formulations of stomatal conductance are validated.

CANDO is being modified to treat effects of water stress, leaf age, and acclimation on photosynthesis. Detailed data on canopy architecture from the tall grass prairie experiments are used as a test of light microclimate, and one-dimensional radiation transfer schemes are compared with three-dimensional schemes. Differences between these schemes are evaluated to determine adequacy for application with different canopies that have substantially different architecture. Problems of scaling leaf level photosynthesis to the canopy of loblolly pine are being examined.

ALLOC describes carbon and nutrient allocation patterns for leaf and stem tissue. Research and modeling continue to search for mechanistic explanations for above- versus below-ground allocation of carbohydrate and nutrient material in plants.

Further validation of SERECO is a priority in the continuation research, which is based on experimental data from the grassland experiments at Kansas State University and from planned Free-Air-CO₂-Exchange experiments with loblolly pine at the Duke Forest. Both types of experiments provide ecosystem level observations suitable for patch scale validation. Also, at the ecosystem level, decomposition and turnover of nutrients are clearly important, and very little information about this ecosystem process exists, as affected by CO₂ and climate change.

The decomposition module is being further developed using results from several experiments now underway. (RPIS 9424)

838. Integration of Experimental and Modeling Approaches in the Unmanaged Ecosystem Research Plan

B.R. Strain

(919) 684-6523

\$484,000

The research objective is to examine the direct physiological effects of CO₂ on plants, with emphasis on long-term effects on the physiology, growth, and ecosystem interactions of loblolly pine. The research produces data for modeling and predicting changes of plant physiology and growth as a function of different future CO₂ and climate conditions. These data include new information from experiments on physiological and ecological controls of whole-plant and whole-system functions. The researchers are developing data on physiology of whole, intact plants.

Under field conditions, researchers are examining physiological controls on plant response to CO₂, with special attention to feedback effects of the plant source-sink carbon balance on the CO₂ assimilation rate. The two phases of research are as follows:

(1) Phase 1 consists of a 2-year partial factorial design experiment with seedlings and saplings to determine if limiting nitrogen and phosphorous affects loblolly pine's response to increase CO₂. Gas exchange (in terms of the A vs. C_i curve), whole plant carbon balance, chlorophyll fluorescence, leaf tissue composition (for CHO, proteins, and nutrients), and rubisco activity are determined as a function of CO₂ treatment.

(2) Phase 2 continues the studies for an additional 3 years to achieve "long-term" data on plant response to increased concentrations of atmospheric CO_2 . The unique feature of this phase is that measurements continue with plants that have been "conditioned" by high CO_2 , which allows researchers to make a realistic and in-depth examination of the degree and mechanisms of plants' photosynthetic acclimation to CO_2 . Moreover, plants are grown in the ground to avoid stresses caused by root confinement.

In addition to carrying out the field research, researchers are assembling existing information about carbon fixation and allocation in plants. This information is used in evaluating ecosystem productivity and stability in relation to CO_2 and climate variables, including nutrient availability and cycling, and in assessing properties of the ecosystem likely to be affected by CO_2 -altered growth (e.g., plant-animal and plant-microbial interactions and water fluxes). This information is used in reexamining the Farquhar equation; it is also used to formulate generic models (e.g., PRECO, SERECO) of whole-plant and whole-system response to CO_2 and climate. (RPIS 9741)

Department of History

839. Spatial and Temporal Patterns of Biotic Exchanges of CO_2 Between the Atmosphere and Tropical Landscapes and their Role in the Global Carbon Balance

J.F. Richards

(919) 684-3626

\$99,000

This research is part of an integrated project to examine terrestrial sources and sinks for atmospheric CO_2 . The six aspects to the work are (1) to determine historical and future spatial-temporal patterns of biotic CO_2 exchange between the tropics and the atmosphere; (2) to determine the long-term (1850–1980) and short-term (1975–1990) annual net tropical carbon flux; (3) to assess the relative importance of mechanisms that control the short-term exchanges; (4) to evaluate the estimated short-term flux using measured variations in atmospheric CO_2 ; (5) to provide a best estimate of tropical CO_2 flux from 1958 to the present; and (6) to test the hypothesis that CO_2 fertilization has been an important mechanism in the net tropical carbon balance.

This component of the integrated project focuses on the first and second items, spatial-temporal patterns of biotic CO_2 exchange, and long-term and short-term net tropical carbon flux. Researchers are producing time-series data on carbon balance for land components (vegetation and soil) in relation to agriculture and increased population in Southeast Asia and Central/South America. The data are used to calculate net CO_2 exchange involving global tropical forests.

The approach provides a historical record of land use, which is important for the first approximation of pre-industrial CO_2 flux from human influences. When combined with fossil fuel CO_2 emissions, these reference data are valuable for modeling the time history of the global carbon cycle. No

alternative approaches exist for reconstructing this type of information. Area figures for land use at each level are converted into estimates of carbon in standing stock of vegetation. These estimates are based upon a large regional ecological and botanical literature measuring biomass for various types of vegetation. (RPIS 10376)

Harvard University

Cambridge, MA 02138

Department of Organismic and Evolutionary Biology

840. Integration of Experimental and Modeling Approaches to Study Competitive Interactions Among Plants Under Elevated CO_2

F.A. Bazzaz

(617) 495-2305

\$265,000

This project obtains data for predicting effects of CO_2 and physical influences (e.g., light, moisture) on plant communities based on knowledge of component species and their growth, productivity response, and resource use. Experimental studies test the hypothesis that CO_2 affects competitive outcome primarily through its influence on utilization of other resources. A priori knowledge of species' response to resource availability and the mechanism of response aids model formulation and development of a predictive capability. Experiments are carried out with mixtures of species representing annual communities and native grasslands. Using CO_2 -controlled growth chambers, the designs examine relative responses at three CO_2 levels; two light intensities; and variable water, nutrient, and temperature conditions. Companion data on physiology provide insight into causes of differential responses to CO_2 . The data are used in a plant competition model to simulate CO_2 effects on community growth and composition change. The initial phase of the research develops a database for annuals for which a mechanistic model of interspecific competition is then formulated. Because the model represents general physiological features, it can be tested with other assemblages of species and/or communities, i.e., the general model structure can serve as a basis for application to mixtures of perennial plants subjected to different levels of CO_2 and different physical environments. A supplemental task of the research is to obtain specific data for modeling community response to CO_2 , temperature, and light. Specifically, experiments characterize the physiological properties of individual leaves throughout the canopy and the lifecycle of co-occurring plant species. Growth and resource deployment are examined as well as CO_2 and light conditions associated with photosynthesis. (RPIS 9298)

University of Illinois

Urbana, IL 61801

Department of Forestry**841. Spatial and Temporal Patterns of Biotic Exchanges of CO₂ Between the Atmosphere and Tropical Landscapes and Their Role in the Global Carbon Balance**

S. Brown

(217) 333-1643

\$103,000

This research is part of an integrated project to examine terrestrial sources and sinks for atmospheric CO₂. There are six aspects to the work: (1) to determine historical and future spatial-temporal patterns of biotic CO₂ exchange between the tropics and the atmosphere; (2) to determine the long-term (1850-1980) and short-term (1975-1990) annual net tropical carbon flux; (3) to assess the relative importance of mechanisms that control the short-term exchanges; (4) to evaluate the estimated short-term flux using measured variations in atmospheric CO₂; (5) to provide a best estimate of tropical CO₂ flux from 1958 to the present; and (6) to test the hypothesis that CO₂ fertilization has been an important mechanism in the net tropical carbon balance.

This component focuses in the third, fifth, and sixth items. More specifically, investigators are determining the biomass of forests and soil carbon that results from land use. Emphasis is placed in tropical American forests.

Investigators are producing a method for converting different types of structural data for forests (inventory of trees by species, diameter, and height from known-size plots; stand and stock tables from large scale forest inventories; stand tables only; and total commercial volumes of forests) into biomass estimates for all the tropical region. More accurate and precise biomass estimates for tropical American forests are being produced. Preliminary models are being developed for predicting forest biomass for areas where no information is available using the Geographical Information System (GIS). Revised estimates of the biomass of tropical forests for all tropical countries based in the commercial volumes reported in the United Nations Food and Agriculture Organization publications and new expansion factors are also being produced. (RPIS 10375)

Kansas State University

Manhattan, KS 66506

Department of Agronomy**842. Rangeland-Plant Response to Elevated CO₂**

C.E. Owensby

(913) 532-5731

\$262,000

The goal of this project is to determine the extent to which C₄-dominated grassland sequesters carbon and acts as a buffer against future increases in atmospheric CO₂. Utilizing ambient and double ambient atmospheric CO₂ concentrations, investigators have defined the following specific objectives for this project: (1) monitor above- and below-ground biomass accumulation and analyze growth dynamics of the principal C₃ and C₄ species (*Andropogon gerardii* and *Poa pratensis*); (2) characterize chemical constituents important to decomposition rates of above- and below-ground biomass; (3) determine net canopy carbon fixation and measure differential responses of leaf level photosynthesis of the principal C₃ and C₄ species to water stress, temperature, and light regimes; (4) measure soil microbial biomass and soil respiration; and (5) estimate carbon source/sink relationships using pulse labeling with carbon isotope and use the Century Model to simulate short- and long-term effects of elevated CO₂ on carbon source/sink relationships. Data on the physiology and plant growth of representative species of the grassland are being obtained. Measurements of carbon fixation and below-ground productivity provide the basis for estimates of carbon transformation into soil humus.

The experiments are conducted in situ in undisturbed prairie. Investigators have chosen five approaches for achieving the different objectives:

(1) Above-ground biomass and growth rate are determined by clipping and separation of plant material by species and component parts. Below-ground productivity is determined from root ingrowth into buried sandbags.

(2) and (4) Carbon turnover, microbial metabolism, and carbon source/sink relationships are estimated from measures of soil respiration and decomposition of organic residues (plant and microbial material). Microbial biomass is determined by fumigation incubation techniques, and soil respiration is measured by trapping soil-generated CO₂ in minichambers.

(3) Carbon fixation and water flux are measured for the intact whole canopy, as well as for individual leaves. Leaf level photosynthesis is measured in the field experiment on tillers at three canopy heights, supplemented by intensive laboratory studies of acclimation to elevated CO₂ at controlled light and temperatures.

(5) Isotopic tracer techniques and the Century model are used in studies of soil organic matter dynamics and for specific estimates of net carbon retention in soil. These data, coupled with observations of CO₂ fixation rates by plants, provide generic information on the carbon balance of grassland ecosystems and their possible influence on sequestering of atmospheric CO₂. (RPIS 9277)

National Aeronautics and Space Administration

New York, NY 10025

Goddard Institute for Space Studies

843. Spatial and Temporal Patterns of Biotic Exchanges of CO₂ Between the Atmosphere and Tropical Landscapes and Their Role in the Global Carbon Balance

I.Y.-S. Fung

(212) 678-5590

\$109,000

This research reduces the uncertainty related to estimates of the net flux of carbon between terrestrial ecosystems and the atmosphere due to deforestation and natural feedbacks in the tropics. A justified reanalysis of the net flux of carbon to the atmosphere as a result of anthropogenic changes and natural atmospheric/biospheric feedbacks, especially in the tropics, is being obtained. The reanalysis involves the use of all available flux data and is constrained by the observed concentrations and gradients of atmospheric CO₂ and its isotopes.

The atmospheric, oceanic, and terrestrial reservoirs have different isotopic signatures. Fractionation effects on the different exchange processes are also distinct. The trends and distributions of the isotopic concentration of CO₂ in all three reservoirs thus provide additional information about CO₂ exchanges.

The three-dimensional atmospheric transport model of the Goddard Institute for Space Studies is being used to simulate atmospheric CO₂ and ¹³CO₂ response to refined estimate of carbon fluxes. The modeled concentrations and gradients are being compared with those observed. (RPIS 10378)

Natural Environment Research Council

Surrey GU8 5UB, United Kingdom

Institute of Oceanographic Sciences

844. Simulations of the Carbon Cycle in the Oceans

M. Fasham, Jr.

011-44-428-794141

\$102,000

Three related components of research are necessary for developing a three-dimensional model of the ocean carbon cycle. The overall goal is to develop a prognostic model of the ocean carbon cycle that can be used to predict future increases of atmospheric CO₂ from human activities. The objectives of the Institute of Oceanographic Sciences component of the project are (1) to develop three-dimensional models of the ocean carbon cycle and to test a carbon/nitrogen mixed-layer ecosystem model against data sets for the North Atlantic; (2) to analyze carbon/nitrogen ecosystem components for a three-dimensional North Atlantic simulation; and (3) to imbed equations of the North Atlantic ecosystem model into the three-dimensional ocean general circulation model and to extend the ecosystem to deeper ocean layers.

This research predicts the role of biological populations in the uptake and recycling of CO₂ in the upper ocean, using simple coupled carbon and nitrogen ecosystem models. Models of gradually increasing complexity are tested by using integrated mixed-layer or one-dimensional models of the physical processes and comparing the results with suitable data sets. The resulting models and their associated parameter sets are then embedded in various three-dimensional physical models developed at Princeton University for predicting basin scale and global effects. The ultimate aim is to develop a model that is geographically robust in the sense that a single model and parameter set coupled with geographically varying physical forcing reproduces the observed variability in biological production and CO₂ uptake. (RPIS 10347)

University of New Hampshire

Durham, NH 03824

Complex Systems Research Center

845. Spatial and Temporal Patterns of Biotic Exchanges of CO₂ Between the Atmosphere and Tropical Landscapes and Their Role in the Global Carbon Balance

D.L. Skole

B. Moore, III

(603) 862-1792

\$105,000

This research is part of an integrated project to examine terrestrial sources and sinks for atmospheric CO₂. Six aspects to the work are (1) to determine historical and future spatial-temporal patterns of biotic CO₂ exchange between the tropics and the atmosphere; (2) to determine the long-term (1850-1980) and short-term (1975-1990) annual net tropical carbon flux; (3) to assess the relative importance of mechanisms that control the short-term exchanges; (4) to evaluate the estimated short-term flux using measured variations in atmospheric CO₂; (5) to provide a best estimate of tropical CO₂ flux from 1958 to the present; and (6) to test the hypothesis that CO₂ fertilization has been an important mechanism in the net tropical carbon balance.

This component of the integrated project focuses on the first and fourth items, spatial-temporal patterns of biotic CO₂ exchange and short-term CO₂ flux. Using satellite observations (e.g., Landsat, AVHRR), researchers are producing maps and spatial integration of data on forest composition and areas of land use change. These data are combined with biomass data to estimate carbon changes. The data also contribute to the Geographic Information System and are used to calculate net CO₂ exchange involving global tropical forests.

Observation from space is used to detect change in the landscape distribution of vegetation; it is an expedient and cost-effective way of determining the quantitative areal changes of land use. The areal changes represent an important term in the equation for first approximation estimates of carbon stocks for tropical forests. (RPIS 10377)

Princeton University

Princeton, NJ 08540

Geophysical Fluid Dynamics Program

846. Simulations of the Carbon Cycle in the Oceans

J.L. Sarmiento
(609) 452-6585

\$288,000

There are three related components of research necessary for developing a three-dimensional model of the ocean carbon cycle. The overall goal is to develop a prognostic model of the ocean carbon cycle that can be used to predict future increases of atmospheric CO₂ from human activities. The objectives of the Princeton component of the project are (1) to develop three-dimensional models of the ocean carbon cycle and to perform the fixed atmospheric CO₂ simulation with nonseasonal and seasonal ocean circulation; (2) to predict background total carbon fields and use a seasonal three-dimensional North Atlantic ecosystem model to do carbon and nitrogen simulations; and (3) to perform simulations with global carbon cycle ecosystem models and to estimate anthropogenic CO₂ uptake by oceans. Three-dimensional ocean model simulations of the uptake of anthropogenic CO₂, including possible feedback effects from changes in the ocean carbon cycle, are being produced.

The research strategy involves two parallel approaches. The first assumes that the pre-anthropogenic ocean carbon cycle continues to operate without being affected directly by anthropogenic perturbations. This "steady state" approach enables investigators to treat the anthropogenic CO₂ as a passive tracer. The only information investigators need regarding the carbon cycle, other than the appropriate thermodynamic constants, is the pre-anthropogenic surface total carbon and alkalinity concentrations.

The second approach that the oceanic carbon cycle is responding dynamically to is the effect of the anthropogenic greenhouse gas perturbations on climate. Princeton University investigators have primary responsibility for placing ecosystem models developed at the Institute of Oceanographic Sciences into ocean circulation models. (RPIS 10346)

San Diego State University

San Diego, CA 92182

Department of Biology

847. Response of Tundra Ecosystems to Elevated Atmospheric Carbon Dioxide

W.C. Oechel
(714) 265-6767

\$300,000

This project has two main objectives: (1) to determine current patterns of CO₂ flux from tussock and wet coastal tundras along environmental gradients on the North Slope of Alaska at sites representing a range of vegetation types and environmental conditions, and to evaluate recent patterns of peat accumulation

in tussock and wet coastal tundras; and (2) to determine methane content of permafrost and current rates of methane release as a function of vegetation and environment. A definitive statement of what is known and unknown about tundra response to varying CO₂ and climate conditions is being produced. This statement includes documentation of logic and supporting data, including measurements of CO₂ and CH₄ exchange across tundra ecosystems.

The research evaluates current rates of CO₂ and CH₄ flux along a latitudinal gradient from the foothills of the Brooks Range to the coast of the Arctic Ocean. Measurements are made along the transect formed by the Haul Road and at other sites where permafrost temperature research has been done on the north slope. Peat profile dating is performed at the same sites as the CO₂/CH₄ flux measurements to compare past and current rates of carbon accumulation or loss.

Field research is carried out with small pop-on chambers to measure CO₂ and CH₄ fluxes with different ecosystems across the North Slope of Alaska. Simultaneously, environmental parameters (air temperature, radiation, RH, soil moisture, and temperature) are determined during the short-term gas exchange experiments. In addition, continuous monitoring of the physical environment is done at the three sites. Ecosystem data (leaf area, aboveground biomass, carbon content of thaw layer, and depth to permafrost) are determined simultaneously with the flux measurements. Initial interpretations relate CO₂ and CH₄ fluxes to environmental and biotic properties of the systems under observation. (RPIS 9586)

Scripps Institution of Oceanography

La Jolla, CA 92093

848. A Study of the Abundance and ¹³C/¹²C Ratio of Atmospheric Carbon Dioxide and Oceanic Carbon in Relation to the Global Carbon Cycle

C.D. Keeling
(619) 534-4230

\$275,000

The project objectives are to continue high precision and accuracy measurements of atmospheric CO₂ at the Mauna Loa Observatory and to expand measurements of ¹³C/¹²C isotopic ratios of CO₂ for distinguishing the biological and oceanic carbon processes undergoing change. This project produces a database for calibrating atmospheric CO₂ circulation models and for evaluating sources and sinks of exchange with oceans and the terrestrial biosphere.

High precision CO₂ and isotopic measurements are carried out at background air pollution monitoring stations of the Central Pacific region, e.g., the Mauna Loa, Hawaii location. Atmospheric CO₂ data are collected at additional sites to create a database for validating three-dimensional models of atmospheric and oceanic transport of carbon in the atmosphere and oceans. These models are used to predict atmospheric CO₂ in relation to changing processes and properties of the global carbon cycle. (RPIS 10194)

Smithsonian Institution Edgewater, MD 21037

Smithsonian Environmental Research Center

849. A Field Study of the Effects of Elevated Ambient CO₂ on Ecosystem Processes in Chesapeake Bay Wetlands

B.G. Drake

(301) 261-9796

\$240,000

This research focuses on the physiological effects of elevated CO₂ on carbon metabolism and on how altered plant metabolism affects ecosystem processes. Mechanistic biophysical information is provided on the response of a wetland plant community when continuously exposed to elevated CO₂. Objectives are to determine whether elevated ambient CO₂ concentration (1) affects ecosystem production through increased photosynthesis and reduced respiration, (2) alters species composition, (3) alters relative partitioning of biomass between aboveground and belowground structures, (4) changes carbon and nitrogen concentration in plant tissue, (5) alters decomposition rates, and (6) changes the water balance in plants and plant communities of a mesohaline salt marsh on Chesapeake Bay.

In addition, researchers are producing a database for modeling the effects of CO₂ enrichment on ecosystem processes, specifically community photosynthesis, carbon accumulation, and change in species composition.

Long-term research continues at the Smithsonian Environmental Research Center, a salt-marsh research site near Edgewater, Maryland. Three community types are being investigated in the field, where an elevated CO₂ level is controlled by small replicated open-top chambers. (RPIS 9437)

University of South Carolina Columbia, SC 29208

Department of Biology

850. Herbivore Responses to Plants Grown in Enriched CO₂ Atmosphere

D.E. Lincoln

(803) 777-7306

\$71,000

The responses of both host plants and insect herbivores to CO₂ are measured with emphasis on changes of insect consumption and consequent impacts on plants. For plants, the research investigates changes in leaf quality in response to rising CO₂, and especially the changes in alleochemicals and carbon/nitrogen ratio as a basis for estimating changes in leaf consumption by insects. Studies of antibiotic alleochemicals also provide an opportunity to examine genetic control of biochemical pathways and accumulated products. The products are experimental data on insect feeding rates as affected by plant tissue produced at different CO₂ levels. Changes in secondary biochemicals are documented, and feeding rates are determined in relation to

CO₂-altered nutritive and biochemical properties. Three sets of experiments are conducted at the Duke University field study on the response of forest species to CO₂: (1) the response of sawfly to loblolly pine needle biochemistry when the plants are field-grown in elevated CO₂, the pine-sawfly system permits an experimental test of the hypothesis that the higher leaf carbon content in elevated CO₂ is a primary determinant of altered insect performance; (2) experimental manipulation of nutrient supply to pine and poplar trees is used to evaluate insect larval performance at different carbohydrate/protein (e.g., different C/N) ratios of leaves; (3) as CO₂ treatment changes carbon source/sink relationships and the formation of plant biochemicals, detailed biochemical and molecular methods are employed to determine chalcone synthase activity, mRNA levels, and flavonoid and tannin content. Molecular studies of chalcone synthase are used because it is a key regulatory enzyme of flavonoid biosynthesis, which subsequently controls the level of the alleochemicals such as phenolics and terpenes in leaves. (RPIS 10622)

State University of New York, Syracuse Syracuse, NY 13210

College of Environmental Science and Forestry

851. Spatial and Temporal Patterns of Biotic Exchanges of CO₂ Between the Atmosphere and Tropical Landscapes and Their Role in the Global Carbon Balance

C.A.S. Hall

(315) 470-6870

\$149,000

This research finishes refining the methods used to predict large scale spatial patterns of land use change, converts models of global carbon flux and land use change into a Geographical Information System format, and applies them to Southeast Asia and Central America.

Many more spatially refined estimates of carbon release as a consequence of land use change are being obtained. These spatial analyses are being used with a geographic-based atmospheric mixing model to further refine the estimates of carbon uptake of other researchers. Large scale geographic data can now be obtained, converted, and used in simulation models that describe past geographical patterns as well as predict future patterns of land use change and carbon exchange.

The description of historical patterns of land use change has been emphasized to validate the land use change predictor. Most spatial work to date has been based on historical maps and digital mapmaking. In the future, satellite imagery will also be incorporated into analyses. Efforts include three components: (1) the preparation of digital maps of elevation, vegetation, and land use; (2) the application and sensitivity analysis of a computer model (GEMOD) that predicts the spatial pattern and temporal dynamics of land use types for a given region and that is made to be interactive with digitized maps or images; and (3) the presentation of results. (RPIS 10374)

Tuskegee Institute

Tuskegee, AL 36088

Department of Agricultural Sciences**852. Effects of Enriched CO₂, Water, and Nutrient Stress on Sweet Potatoes: Towards the Development of a Universal Crop Simulation Model***P.K. Biswas*

(205) 727-8452

\$66,000

Field experiments are being carried out at Tuskegee Institute to determine (1) interaction of water stress with CO₂ enrichment on field-grown sweet potatoes, including growth, yield, physiology, rhizosphere biochemistry, and soil microbial activity; (2) interaction of nutrients (nitrogen, phosphorous, and potassium) with CO₂ enrichment, looking at the same endpoints; and (3) interaction of potassium only with CO₂ enrichment, looking at the same endpoints as the previous two studies. New data on physiology and growth of sweet potatoes are being provided from these field studies. Interactive effects of CO₂, water, and nutrient stress are being determined.

The field experiments are carried out with open-top chambers, which have been well-calibrated for this type of research. The experimental design examines physiology and growth differences as a function of different CO₂ concentrations. The experiments produce data on physiological, photosynthetic, and biochemical characteristics of the sweet potato in relation to variations in CO₂ concentration when combined with different water and nutrient treatments. Researchers examine growth, morphological, physiological, and rhizosphere biochemistry responses to the different treatments. The research focuses on an apparent potassium deficiency that is often observed when plants are grown at elevated CO₂. (RPIS 9626)

Woods Hole Research Center

Woods Hole, MA 02543

853. Spatial and Temporal Patterns of Biotic Exchange of CO₂ Between the Atmosphere and Tropical Landscapes and Their Role in the Global Carbon Balance*R.A. Houghton*

(617) 540-9900

\$225,000

This research is part of an integrated project to examine terrestrial sources and sinks for atmospheric CO₂. There are six aspects to the work: (1) to determine historical and future spatial-temporal patterns of biotic CO₂ exchange between the tropics and the atmosphere, (2) to determine the long-term (1850–1980) and short-term (1975–1990) annual net tropical carbon flux, (3) to assess the relative importance of mechanisms that control the short-term exchanges, (4) to evaluate the estimated short-term flux by using measured

variations in atmospheric CO₂, (5) to provide a best estimate of tropical CO₂ flux from 1958 to the present, and (6) to test the hypothesis that CO₂ fertilization has been an important mechanism in the net tropical carbon balance.

This component of the integrated project focuses on the fifth item, tropical CO₂ flux. Current estimates of the net flux of carbon to the atmosphere from tropical deforestation and reforestation range between 0.5 and 2.5 x 10¹⁵ g for 1980. The products of this research are a refined range of estimates for the 1980s and new estimates of the integrated flux between 1850–1990.

In approaching this research, existing statistics on carbon content of vegetation and soils are assembled, and a simple carbon balance model is used to estimate CO₂ flux. The analysis concentrates on changes involving tropical forests; however, the estimates are combined with data from other geographic areas to provide a global estimate of the CO₂ flux from land clearing and other human influences. As new data are reported in the open literature, they are promptly incorporated into the global CO₂ analysis. (RPIS 10373)

Global Change: Oceans Research**Intramural DOE Laboratories****Brookhaven National Laboratory**

Upton, NY 11973

Oceanographic and Atmospheric Sciences Division**854. Diagnostic Analysis of Iron Limitation of CO₂ Uptake by Oceanic Phytoplankton***P.G. Falkowski*

(516) 282-2961

\$82,000

The objective of this project is to develop a diagnostic technique(s) to determine iron limitation of phytoplankton production. The project uses a variety of techniques—biophysical, biochemical, and microbiological—to assess the effects of iron deficiency on phytoplankton. Controlled laboratory studies using iron-limiting chemostat cultures provide basic information on the response of the photosynthetic apparatus to iron limitation. Intraspecific comparisons are made between phytoplankton from two taxonomic groups—diatoms and coccolithophorids. Field studies in the southern oceans using natural phytoplankton populations are conducted to determine whether natural iron concentrations restrict phytoplankton biomass and productivity. The product of the research is the ability to assess any iron or other trace metal nutrient quantitatively in sub-Arctic and Antarctic surface ocean waters. (RPIS 5506)

Oceanographic Sciences Division

855. Inorganic Carbon Measurements for the World Ocean Circulation Experiment—Hydrographic Program

D.W.R. Wallace

K. Johnson

(516) 282-2945

\$442,000

This project collects comprehensive, intercomparable, high quality CO_2 data on samples collected during the World Ocean Circulation Experiment-Hydrographic Program (WOCE/HP) one-time survey in the Atlantic Ocean. These data are required for estimating carbon fluxes in the ocean and for understanding the relationship between CO_2 and climate. Shipboard analysts on WOCE/HP cruises analyze almost all water samples for dissolved inorganic carbon (DIC), pH, and partial pressure of CO_2 ($p\text{CO}_2$). DIC is measured by automated coulometric titration; $p\text{CO}_2$ by headspace catalytic gas chromatography with flame-ionization detection; and pH, by a specially designed pH cell interfaced to the coulometric system. These state-of-the-art methods have been selected to yield the highest possible precision, accuracy, and processing efficiency for the greatest number of samples at sea. In addition to inorganic CO_2 measurements, the basic biomass parameters chlorophyll *a*, particulate organic carbon and nitrogen, and depth of the euphotic zone are measured during selected cruises. These field measurements allow carbon cycling to be related to remotely sensed variables such as chlorophyll. The project's end products are inorganic carbon and basic biomass data sets in sufficient density to allow calculation of carbon fluxes and storage using water mass transport and ocean circulation models. (RPIS 5374)

Oak Ridge National Laboratory

Oak Ridge, TN 37831

Environmental Sciences Division

856. Oceanic Uptake of Carbon Dioxide

T.-H. Peng

(615) 574-0390

\$110,000

To improve the quantitative understanding of atmosphere-ocean CO_2 interactions and produces an estimate of the potential for the world oceans to assimilate increases in atmospheric CO_2 during the next century, two tasks are being performed. The first task examines dynamic constraints on CO_2 uptake by the iron-fertilized Antarctic Ocean through model simulation. With dynamic considerations based on the distribution of bomb-produced ^{14}C , the second involves seasonal variation in $p\text{CO}_2$ and its effect on global CO_2 uptake. The measured difference between ocean surface $p\text{CO}_2$ and atmospheric $p\text{CO}_2$ represents the thermodynamic potential for driving the transfer of CO_2 gas across the sea-air interface. Unfortunately, data describing the distribution of $p\text{CO}_2$ are limited to a small fraction of the world oceans. Previous research used sea surface temperature to

estimate $p\text{CO}_2$ values under various oceanographic regimes. Recent measurements of seasonal variation in sea surface properties near Iceland, combined with model results for seasonal $p\text{CO}_2$ values, demonstrate that variations in surface $p\text{CO}_2$ are more strongly correlated to nutrient concentrations than water temperatures. To improve upon the previous estimates, it may be possible to exploit relations between spatial oceanic estimates of $p\text{CO}_2$ and existing nutrient concentration data. Nutrient concentrations in the surface mixed layer are routinely measured during most oceanographic expeditions. One likely potential nutrient surrogate is the oceanic surface PO_4 concentration, which has been widely measured. Thus, the approach for this task entails establishing regional relationships between $p\text{CO}_2$ and PO_4 for the world oceans, relying primarily on world ocean $p\text{CO}_2$ data are stored at LDGO. Winter and summer maps of the global distributions of delta $p\text{CO}_2$ are constructed and used to refine the calculations of net CO_2 uptake by the world oceans. (RPIS 5518)

Pacific Northwest Laboratory

Sequim, WA 98328

Battelle Marine Sciences Laboratory

857. Carbon Dioxide Ocean Research

J.P. Downing

(206) 683-3607

\$1,700,000

The objectives of this project are to (1) implement Phase I of the Ocean Research Plan completed in August 1989, (2) begin the global survey of carbon dioxide in the ocean (special research grant program 89-7A), and (3) establish the science team for the program. Four major products are being produced by this project: (1) a paper presented at Ocean Instrumentation '90, held in San Diego, March 1990, "A SMART, Expendable Conductivity-Temperature-and-Depth Profiler — AXCTD," (2) a working prototype AXCTD with ARGOS satellite data telemetry link, (3) a Carbon Dioxide Research Program Technical Report: *An Evaluation of Surface Ocean Models for Climate Research*, and (4) numerous short technical reports to assist the ACRD with the Committee on Earth Sciences (CES) and interagency coordination of ocean research. Phase I of the Ocean Research Plan is being implemented. This phase includes process studies, data analysis, and ocean model development designed to improve existing ocean simulation and prediction capabilities. These activities are conducted in anticipation of large multiagency ocean observations to be conducted in the 1990s, such as the World Ocean Circulation Experiment and the Joint Global Ocean Flux Study. The results will provide a better framework to analyze the large data streams expected over the 5–10 year lives expected of these programs. (RPIS 4862)

Global Change: Oceans Research

Offsite Grants

Columbia University

Palisades, NY 10964

Lamont-Doherty Geological Observatory

858. Steady-State and Transient Modeling of Tracer and Nutrient Distributions in the Global Ocean

W.S. Broecker

(914) 359-2900

\$118,000

The objective of this project is to diagnose the time-dependent relationship between ocean circulation and biological activity relative to the ocean carbon cycle. The research will provide new information on the interaction between ocean circulation, biological activity, and the carbon cycle and a tool to explore the transient behavior of this interaction. A two-dimensional, zonally averaged ocean model is being extended to include ocean tracers and nutrients. Inclusion of the ocean tracers assists in the validation of the model and in the diagnosis necessary to improve the model capabilities. The transient behavior of the tracer distributions is being analyzed. This transient calculation includes the interaction of the ocean circulation and tracer/nutrients as greenhouse-gas-induced climate change progresses as well as over paleoclimate time scales. First, the data (bomb tritium) are used to constrain the model's dynamics and parameterizations. To capture possible mode changes, the glacial-to-interglacial time scale is investigated. Next, the model is used to study two scenarios for CO₂-induced warming and to conduct a set of experiments to simulate the CO₂ change at the termination of the last ice age. Further, the nutrient cycle is incorporated into the model and validated. The completed model is then used to identify the physical processes governing the ocean uptake of CO₂. This information is used to tune the nutrient/physical interactions within the model. Dissolved oxygen experiments are used as a final check on the model before conducting experiments and analyses to characterize how the dynamics of the ocean influence the nutrient cycle during climate change. (RPIS 10513)

859. CO₂ Measurements Along the World Ocean Circulation Experiment P-16 and 19 Sections in the South Pacific Ocean: A Joint Lamont-Doherty Geological Observatory/Woods Hole Oceanographic Institution Program

T. Takahashi

(914) 359-2900

\$137,000

The project objective is to contribute accurate data on the carbon chemistry of seawater to a global oceanic database for numerical modeling. The project will produce a data report of tabulated carbon chemistry properties of south Pacific Ocean seawater and an evaluation of the compatibility of total carbon

dioxide CO₂ and alkalinity measurements made by different methods. Three carbon chemistry properties are measured in seawater from the south Pacific Ocean during the World Ocean Circulation Experiment (WOCE) P-16 and P-19 expeditions. Measurements of total CO₂ and partial pressure of CO₂ from at least one-third of the 440 WOCE sampling stations, yield a profile of carbon chemistry with depth in the South Pacific. At least two samples of the surface mixed layer are analyzed at every station. Total CO₂ is determined using a coulometer aboard ship, and alkalinity analyses will be performed ashore as companion measurements for radiocarbon measurement by accelerator mass-spectrometer at Woods Hole Oceanographic Institution. Samples are analyzed for total CO₂ by coulometric and manometric methods, under a separate grant, to resolve disagreement between the methods and to evaluate the compatibility of coulometric and manometric total CO₂ data. CO₂ partial pressure is determined aboard ship using an equilibrator-gas chromatograph system. Seawater samples are stored for onshore alkalinity determinations by potentiometric acid titration. If possible, the CO₂ chemistry data sets will be produced in a gridded format for numerical modeling. Because there are virtually no carbon measurements for either the surface or deep water of the South Pacific Ocean, the total CO₂, CO₂ partial pressure, and alkalinity measurements made during this project will fill an important data gap. (RPIS 10258)

860. Measurements of Carbon Dioxide in the Southern Ocean Along the World Ocean Circulation Experiment S-4 Section

T. Takahashi

(914) 359-2900

\$169,000

The project's objectives are (1) to determine accurately the carbon chemistry of seawater and (2) to contribute to a global oceanic database for numerical modeling. The product is a data report of tabulated total CO₂ concentrations and CO₂ partial pressure in seawater from the Pacific sector of the Southern Ocean. The total CO₂ concentration and CO₂ partial pressure in seawater are measured in seawater from the Pacific sector of the Southern Ocean along the World Ocean Circulation Experiment S-4 lines, 67 S. Measurements of total CO₂ and partial pressure of CO₂ from about one-third of the 110 sampling stations yield depth profiles of carbon chemistry in the Pacific Ocean. At least two samples of the surface mixed layer are analyzed at every station. Aboard ship, total CO₂ is measured with a coulometer, and CO₂ partial pressure is determined with an equilibrator-gas chromatograph system. Because virtually no carbon measurements exist for either the surface or deep water of these areas of the Southern Ocean, the total CO₂ and pCO₂ to be made during this project fill an important data gap. (RPIS 10626)

National Academy of Sciences Washington, DC 20418

861. Ocean Studies Board

M.H. Katsouras
(202) 334-2714

\$50,000

The Ocean Studies Board (OSB) provides scientific leadership and guidance to the Federal Government on important national and international issues in the ocean sciences. Current Board activities are concentrated in two main areas:

(1) The Carbon Dioxide Panel is focusing its attention on the issues of (1) oceanic CO_2 measurements, calibration, and data; and (2) CO_2 gas exchange across the air-sea interface. The Panel is addressing the issue of seawater CO_2 standards that are now being developed for the World Ocean Circulation Experiment and the Joint Global Ocean Flux Study. Management of oceanic CO_2 data is also being addressed. The Panel is also convening a workshop on the topic of the exchange of CO_2 across the air-sea interface.

(2) The Committee on the Ocean's Role in Global Change is following up its 1990 report *The Ocean's Role in Global Change: The Contemporary System* with a report on the geological elements of global change. The Committee also serves as the liaison between the U.S. marine research community and the international Committee on Climatic Change and the Ocean.

OSB serves as the National Research Council's focal point for the consideration of ocean issues. Board members identify, address, and develop studies on appropriate science and policy issues; additionally, they respond to specific requests from Federal agencies and private foundations. Ad hoc or standing committees are established as required.

OSB comprises 18 regular members and 4 liaison members. It meets approximately three times a year to review its activities, provide a forum for presentation and discussion of information about Federal oceanographic research and development programs, identify issues needing scientific input, and assist in the development of U.S. positions on international ocean science matters.

The Board is a multidisciplinary body with members from the fields of physical oceanography, marine ecology and geophysics, marine biology, marine chemistry, and social sciences. The Board conducts much of its work through committees, working groups, and panels. Members are drawn from academic institutions, industry, and national laboratories. (RPIS 10188)

Scripps Institution of Oceanography La Jolla, CA 92093

862. The Quality Control of Oceanic Carbon Dioxide Measurements: Preparation and Distribution of Reference Materials

A.G. Dickson
(619) 534-2582

\$237,000

The project's four objectives are to (1) develop and provide reference materials for carbon dioxide in sea water; (2) coordinate and develop standard measurement procedures; (3) provide quality control guidance for measurements; and (4) develop an automated, ultraprecise pH method to monitor the long-term stability of reference materials. This research provides the reference materials (RMs) necessary to ensure that CO_2 analyses made by several laboratories, working independently at sea, are consistent. The research has four components. The major effort is to prepare and bottle reference materials for total dissolved inorganic carbon (C_T) and alkalinity (A_T). Four to six batches of RM (depending on cruise schedule and at-sea requirements) are produced, certified, and distributed each year of the project. RMs are distributed to Department of Energy (DOE) survey participants as well as to investigators in the Joint Global Ocean Flux Study (JGOFS) time-series program and foreign laboratories working on international World Ocean Circulation Experiment (WOCE) ships. The Scripps team tracks and documents the performance of the RMs. In conjunction with other research supported by the National Science Foundation, the second component is to support an ongoing, collaborative study of C_T analytical procedures and to initiate similar studies for A_T , pH, and CO_2 fugacity ($f(\text{CO}_2)$). The third component is to provide guidance on quality control of the global CO_2 survey and to assist with the crosschecking of calibration standards among WOCE and JGOFS analysts. To do this, the DOE Handbook of Methods is revised, maintained, and distributed to DOE, JGOFS, and other investigators involved with oceanic CO_2 measurements. The fourth component includes the development and application of an automated, ultraprecise pH method to monitor the long-term stability of RMs distributed during the DOE survey. The data generated by this research are incorporated in the ocean CO_2 data package being assembled by the Carbon Dioxide Information and Analysis Center at Oak Ridge National Laboratory. (RPIS 10655)

863. Oceanic CO_2 Measurements for the World Ocean Circulation Experiment Hydrographic Survey in the Pacific Ocean, 1990-1991: Shore-Based Analysis During LEG 1-3

C.D. Keeling
(619) 534-4230

\$47,000

The project objective is to conduct shore-based measurements of dissolved inorganic carbon (DIC) and titration alkalinity on approximately 10 percent (1,400) of the seawater samples collected at sea along World Ocean Circulation Experiment/

HP lines P-16 and P-19 in the equatorial and southern Pacific Ocean. Seawater samples are collected, many in duplicate, and preserved aboard ship. Onshore, the samples are analyzed by the Carbon Dioxide (CO_2) Research Group at Scripps Institution of Oceanography. Precise and rigorously calibrated measurements are made of dissolved inorganic carbon by manometric analyses and of alkalinity by potentiometric titration. The manometric carbon analysis is compared to results of shipboard coulometric analysis. Where possible, shore-based alkalinity measurements are compared to shipboard measurements of alkalinity at the time of collection. Values of CO_2 partial pressure are calculated using measured DIC, alkalinity, as well as salinity, temperature, and nutrient data. The calculated CO_2 partial pressures are compared to direct shipboard measurements of CO_2 partial pressure (by equilibration/gas chromatography). The combined shore data and shipboard measurements of carbon chemistry provide the database necessary for improving estimates of CO_2 cycling in the ocean. (RPIS 10259)

864. Oceanic CO_2 Measurements for the World Ocean Circulation Experiment Hydrographic Survey of the Pacific Ocean: Shipboard Alkalinity Analyses During 1991 and 1992

C.D. Keeling

(619) 534-4230

\$150,000

The objective of this project is to conduct shipboard measurements of titration alkalinity on sea water samples collected along World Ocean Circulation Experiment (WOCE/HP) lines in the equatorial and southern Pacific Ocean and to use the resulting data in conjunction with CO_2 partial pressure (pCO_2), dissolved inorganic carbon (DIC), and shore-based alkalinity measurements. The eventual product of this research will be internal consistency and reliability of oceanic CO_2 data. Titration alkalinity (ALK) of sea water samples obtained along WOCE lines in the Pacific Ocean is determined at sea by potentiometric acid titration. The ALK titrations are made in conjunction with measurements of DIC by other DOE-supported shipboard teams. The ALK data are compared with measurements underway of pCO_2 made by equilibrator/gas chromatography and with shore-based DIC and ALK measurements on replicate water samples. The combined data set provides a critical test of the thermodynamic equations used to connect pCO_2 , DIC, and ALK. (RPIS 10427)

865. Acoustic Global Warming Feasibility Experiment

W. Munk

R. Spindel

T. Birdsall

(619) 534-2877

\$150,000

The project objective is to test the feasibility of ensonifying a global array of underwater hydrophones with a single acoustic source in order to demonstrate the potential for directly measuring the rate of warming of the global ocean. Specifically, this project tests signaling schemes and acoustic

path reliability. The project provides a new characterization of long range acoustic transmissions in the oceanic sound channel, determination of optimal signaling schemes, and analysis of ray path structure, travel times, and ocean temperature. Feasibility experiment results and analyses will be presented in a journal article. Obtaining direct atmospheric measurements of surface warming is difficult because of wide fluctuations in the ambient background air temperature. In contrast to the atmosphere, oceanic temperature fluctuations due to mesoscale, seasonal, and decadal variations are much reduced, suggesting a robust environment for detecting long-term global temperature trends. This experiment tests the idea that travel time of acoustic energy between a source and receiver depends on the sound speed, which in turn is determined primarily by water temperature. Acoustic signals are transmitted for 7 days from a location near Heard Island in the south Indian Ocean to receivers off the eastern and western coasts of the U.S., each a distance of about 16,000 km, and to receivers in New Zealand, Christmas Island, and possibly Mawson Station in Antarctica, to determine whether received signal-to-noise levels are sufficiently high to measure arrival times to a required 10 to 20 ms precision. The impact of the signal on marine mammals is also being studied. This experiment is conducted by Scripps Institution of Oceanography, the University of Michigan, and the Applied Physics Laboratory of the University of Washington. It is jointly supported by DOE, ONR, National Science Foundation, and the National Oceanic and Atmospheric Administration. Ten other nations are also participating. (RPIS 10246)

866. Central Equatorial Pacific Experiment

V. Ramanathan

(619) 534-6381

\$1,200,000

The project objective is to understand the radiative feedbacks and energy fluxes in the tropical western Pacific and use this understanding to advance climate model development, i.e., to test the validity of the thermostat hypothesis. The products of the research include aircraft data sets and satellite data sets. These products are used with an advanced cloud radiation model and a coupled ocean/atmosphere climate model to determine the validity of the thermostat hypothesis. In the tropical western Pacific ocean, deep convection occurs throughout the year with cloud tops and depths at a maximum for the Earth. The region also has the warmest sea surface temperatures (SST) on the planet. The coupling of the warm ocean and deep convection transports large amounts of water vapor, the primary atmospheric greenhouse gas, and latent heat throughout the atmospheric column. The cirrus anvils, made up of ice crystals, cover millions of square kilometers. The clouds trap the outgoing infrared radiation, but reduce the incoming solar radiation by up to a factor of 2. The hypothesis is that a "super" greenhouse must be induced by the unique energy balance with the clouds regulating SST, yet owing their existence to the warm SSTs and the convection, a thermostat. The approach is to conduct an intense field measurement campaign in March 1993. Timing is based on the availability of the aircraft as well as scientific consideration. The Tropical Ocean Global

Atmosphere (TOGA) experiment is working in the region. The data sets being obtained as part of TOGA are useful for the Central Equatorial Pacific Experiment (CEPEX) and vice versa. The aircraft include the ER-2 high altitude aircraft and several options for the midaltitude measurements. The principal investigators and colleagues work closely with the Atmospheric Radiation Measurement (ARM) Science Team to assure that the data essential for testing the hypothesis of the super greenhouse effect in the tropical western Pacific can be used to meet ARM objectives in the region. The data include atmospheric profiles of temperature and humidity, estimates of total water vapor, surface data from ships and buoys, up (and down) sondes from balloons (and aircraft), and three-dimensional radiative information for cloud research. (RPIS 10729)

867. Measurements of Surface Ocean Carbon Dioxide Partial Pressure During World Ocean Circulation Experimentation

R.R. Weiss

(619) 534-2598

\$51,000

The project objective is to assess the spatial and temporal roles of the oceans in the global carbon cycle with emphasis on the potential for the ocean to absorb fossil fuel CO_2 . Shipboard measurements of pCO_2 and pN_2O in surface water and the atmosphere are made along approximately three WOCE/HP lines per year. The measurements are made by an automated high precision gas chromatographic system, which measures CO_2 by flame ionization after quantitative reaction to methane in a stream of hydrogen using a reduced nickel catalyst preceded by a palladium catalyst. Nitrous oxide is measured by a separate electron capture detector. The system has the capacity to measure CO_2 and N_2O in the ocean and atmosphere about twice per hour. The project will provide a report with data tables and plots along with data in digital form. (RPIS 10260)

Woods Hole Oceanographic Institution

Woods Hole, MA 02543

Department of Marine Chemistry

868. CO_2 Measurements Along the World Ocean Circulation Experiment P-16 and 19 Sections in the South Pacific Ocean: A Joint Lamont-Dougherty Geological Observatory/Woods Hole Oceanographic Institution Program

C. Goyet

(508) 457-2000

\$273,000

The project objective is to contribute accurate data on the carbon chemistry of seawater to a global oceanic database for numerical modeling. The project will produce a data report of tabulated carbon chemistry properties of South Pacific Ocean seawater and an evaluation of the compatibility of total carbon dioxide (CO_2) and alkalinity measurements made by different methods. Three carbon chemistry properties are being measured in seawater from the south Pacific Ocean along the

World Ocean Circulation Experiment P-16 and P-19 lines. Measurements of total CO_2 and partial pressure of CO_2 from at least one-third of the 440 sampling stations, yield a profile of carbon chemistry with depth in the South Pacific. At least two samples of the surface mixed layer are being analyzed at every station. Total CO_2 is determined using a coulometer aboard ship. Alkalinity analyses are performed ashore; these are companion measurements for radiocarbon measurement by accelerator mass spectrometer at Woods Hole Oceanographic Institution. Samples are analyzed for total CO_2 by coulometric and manometric methods to resolve disagreement between the methods and to evaluate the compatibility of coulometric and manometric total CO_2 data. CO_2 partial pressure is determined aboard ship using an equilibrator-gas chromatograph system. Seawater samples are stored for onshore alkalinity determinations by potentiometric acid titration. If possible, the CO_2 chemistry data sets will be produced in a gridded format for numerical modeling. Because virtually no carbon measurements exist for either the surface or deep water of the south Pacific Ocean, the total CO_2 , CO_2 partial pressure, and alkalinity measurements made during this project will fill an important data gap. (RPIS 10257)

Global Change: National Institute for Global Environmental Change

Offsite Grants

University of California, Davis

Davis, CA 95616

National Institute Office

869. National Institute for Global Environmental Change

C.C. Delwiche

(916) 757-3350

\$10,863,000

The institute is operated for DOE through a cooperative agreement with the University of California. In addition to the National Institute office located at the University of California, the Institute has five Regional Centers: Northeastern Regional Center hosted by Harvard, Midwestern Regional Center hosted by Indiana University, Southcentral Regional Center hosted by Tulane, Southeastern Regional Center hosted by The University of Alabama, Tuscaloosa, and the Western Regional Center co-hosted by the University of California (UC), Davis and UC, Irvine. Each Regional Center adopted research thrusts in FY 1992 to focus on significant global change features of their geographical region, and to provide integration and applicability of the information obtained.

The Northeastern Regional Center focuses on the following research thrusts: (1) field studies of factors that influence atmospheric concentrations of greenhouse gases, with emphasis on northern forests and related biomes; (2) reconstruction of recent atmospheres and climate, especially innovative experimental proxy measurements; (3) physical basis for climate change, with emphasis on process studies of dynamical and radiative mechanisms; and (4) analysis, quantitative assessment, and communication of uncertainty about global environmental change, including magnitude of changes, impacts, etc.

The Midwestern Regional Center (1) identifies, measures, and analyzes atmospheric trace gases and aerosols, particularly those with either significant global warming potential or significant ozone depletion potential; (2) improves predictive capability of future responses of global and regional climates to changing atmospheric conditions; (3) identifies and analyzes potential impacts of global environmental change, particularly climate change, on biological productivity in both natural and agricultural systems; (4) identifies and analyzes potential impacts of global environmental change on the quantity and quality of water resources; and (5) analyzes energy production and use policies that have consequences on the sources and sinks of atmospheric trace gases.

The Southcentral Regional Center focuses on (1) prediction and detection of climate change and (2) modeling of sources and sinks of greenhouse gases.

The Southeastern Regional Center researches (1) structure and rates of Southern pine and Appalachian hardwood forest ecosystem processes affecting climate change, (2) atmospheric and marine modeling related to global climate change, (3) uncertainties reductions in global budgets of greenhouse gases, (4) geologic and natural system impacts on global environmental change; and (5) policy/education and analysis methods necessary in assessing the human dimension in causing global environmental change.

The Western Regional Center examines (1) agricultural, hydrological, and ecological effects of global climate change; (2) atmospheric and oceanographic modeling of global climate change; (3) climate forcing by trace gases; and (4) assessment of the impacts of global environmental change, and policy/educational aspects of the human response to such change.

Several characteristics of the third year's research program are worthy of emphasizing. The research thrusts were used to promote integration and synergism among investigators within each region of NIOEC. The cross-cutting theme of atmospheric chemistry linked the Regional Centers. Initial outreach research in the first year allotted a percentage of each Center's funding to institutions other than the host institution.

In spring of 1992, the four Regional Centers completed their request for proposal process within their regions to utilize the FY 1992 funding. For this fiscal year, the goal is again to have at least 50 percent of the funding allocated outside of the host institutions. The Institute's Regional Center Advisory Committee has authorized the NIOEC Director to use a portion of the funds allocated to the institute management entity for especially meritorious endeavors of national significance or uniqueness. Projects funded from FY 1992 resources include (1) development of a radiative and cloud parameterization scheme of stratocumulus and stratus clouds, including the impact of cloud condensation nuclei on cloud albedo, (2) analysis of ultrahigh resolution infrared solar spectra for earth detection of a change in atmospheric opacity, (3) above and below ground ecosystem response to elevated atmospheric CO₂, (4) isotopic studies of the biogeochemical cycle of carbon, and (5) carbonic acid weathering of silicate rocks. (RPIS 1028)

Investigator Index

Abbott, S.B.

National Academy of Sciences, Washington, DC
Polar Research Board, 592
Polar Research Board, 757

Abola, E.E.

Brookhaven National Laboratory, Upton, NY
Protein Data Bank Operations, 264

Acock, B.

U.S. Department of Agriculture-Agricultural Research Service, Beltsville, MD
Simulation Modeling of Crop Response to CO₂ Enrichment, 831

Adams, M.

The Institute for Genomic Research, Gaithersburg, MD
Expressed Sequence Tags from Human Brain cDNAs for Genome Mapping, 370

Adameon, A.E.

Oak Ridge National Laboratory, Oak Ridge, TN
Human Genome Management Information System, 322

Addis, R.P.

Westinghouse Savannah River Company, Aiken, SC
Atmospheric Transport of Contaminants, 562

Adelstein, J.S.

Massachusetts Institute of Technology, Cambridge, MA
Short-Lived Radiopharmaceuticals, 512

Adler, H.I.

Oak Ridge Institute for Science and Education, Oak Ridge, TN
Microbiology, 141

Ainsworth, C.C.

Pacific Northwest Laboratory, Richland, WA
Chemical Desorption, Dissolution, and Partitioning, 646

Aker, P.M.

University of Pittsburgh, Pittsburgh, PA
Characterization of Gas-Aerosol Interaction Kinetics Using Morphology-Dependent Stimulated Raman Scattering, 568

Albertini, R.J.

University of Vermont, Burlington, VT
The Development of In Vitro Mutagenicity Testing Systems Using T-Lymphocytes, 104

Allen, L.H.

U.S. Department of Agriculture—Agricultural Research Service, Gainesville, FL
Assessment of Crop Response to Increased Atmospheric Carbon Dioxide: Rising CO₂ Effects on Rice, 832

Aller, R.C.

State University of New York at Stony Brook, Stony Brook, NY
Multiple Tracer Measurement of the Coupling Between Benthic C Fluxes and Bioturbation Activity During the Spring Bloom, 605

Allison, D.P.

Oak Ridge National Laboratory, Oak Ridge, TN
Using Scanning Tunneling Microscopy to Sequence the Human Genome, 315

Allwine, K.J.

Pacific Northwest Laboratory, Richland, WA
Atmospheric Diffusion in Complex Terrain, 553

Alpen, E.L.

Lawrence Berkeley Laboratory, Berkeley, CA
Long Term Biological Effects: Carcinogenic Effects of High Linear Energy Transfer Radiation, 37

Ambrose, K.R.

Oak Ridge National Laboratory, Oak Ridge, TN
Nuclear Medicine and Biomedical Radioisotope Technology, 478

Amy, P.S.

University of Nevada, Las Vegas, NV
Spatial Variability of Deep Subsurface Micro-Organisms and Correlation with Hydrogeologic Parameters, 670

Anderson, C.W.

Brookhaven National Laboratory, Upton, NY
Control of Gene Expression in Mammalian Cells and Viruses, 110

Anderson, J.R.

University of Wisconsin, Madison, WI
An Experimental Regional Scale Climate Simulation Laboratory, 774

Anderson, N.G.

Large Scale Biology Corporation, Rockville, MD
Instrumentation for Automated Colony Processing, 374

Anderson, P.A.

National Science Foundation, Washington, DC
CEES Working Group on Global Change, 764

Andrews, G.F.

Idaho National Engineering Laboratory, Idaho Falls, ID
Complete Degradation of Mixed Halocarbons by
Methanogenic and Methanotrophic Microbial
Communities, 620

Angel, S.M.

Lawrence Berkeley Laboratory, Berkeley, CA
An Investigation of Chemical Flow Characteristics
Using Fiber Optic Sensor Technology, 627
Lawrence Livermore National Laboratory,
Livermore, CA
Remote Detection of Environmental Contaminants
Using Fiber Optic Spectroscopy, 222

Anzick, S.L.

Los Alamos National Laboratory, Los Alamos, NM
High Precision Mapping of Yeast Artificial
Chromosome Clones onto Chromosome 21 by
Fluorescence In Situ Hybridization and Image
Analysis, 304

Apsell, P.

WGBH Educational Foundation, Boston, MA
The Secret of Life, 402

Arakawa, A.

University of California, Los Angeles, Los Angeles, CA
Development of an Advanced Finite-Difference
Atmospheric General Circulation Model, 741

Arakawa, E.T.

Oak Ridge National Laboratory, Oak Ridge, TN
Physics of Solids and Macromolecules, 182

Arlinghaus, F.

Oak Ridge National Laboratory, Oak Ridge, TN
DNA Sequencing Using Stable Isotopes, 317

Arlinghaus, H.F.

Atom Sciences, Inc., Oak Ridge, TN
Increased Speed in DNA Sequencing by Utilizing
Laser Atomization Resonance Ionization
Spectroscopy and Sputter-Initiated Resonance
Ionization Spectroscopy to Localize Multiple
Stable Isotope Labeled Fragments, 333

Arnold, R.G.

University of Arizona, Tucson, AZ
Transport of Subsurface Biocolloids in
Porous Media, 654

Atcher, R.W.

Argonne National Laboratory, Argonne, IL
Research in Nuclear Medicine, 445

Athwal, R.S.

University of Medicine and Dentistry of New Jersey,
Newark, NJ
Monoclonosomal Hybrids for the Analysis of
the Human Genome, 384

Attwood, D.T.

Lawrence Berkeley Laboratory, Berkeley, CA
Biological X-Ray Microscopy Resource Center, 432

Avissar, R.

Rutgers University, New Brunswick, NJ
An Evaluation of the Appropriate Land-Surface
Resolution for Climate Models, 768

Ayala, F.J.

University of California, Irvine, Irvine, CA
Genetic Variation in Resistance to Ionizing
Radiation, 157

Babic, M.

University of Notre Dame, Notre Dame, IN
Hydrodynamic Controls on Particle Transport
Through Heterogeneous Porous Media, 676

Baer, F.

University of Maryland, College Park, MD
Exploitation of Parallelism in Climate Models, 752

Bakale, G.

Case Western Reserve University, Cleveland, OH
Ionization in Liquids: Electron Transport and
Reactions in Model, Biometric, and
Biological Systems, 195

Baker, M.E.

University of Arizona, Tucson, AZ
Single-Molecule Detection Using Charge
Coupled Device Array Technology, 331

Baker, R.J.

Los Alamos National Laboratory, Los Alamos, NM
Chromosomal Organization of Human Repetitive
DNA Sequences, 307

Balding, D.

Los Alamos National Laboratory, Los Alamos, NM
Pooling Yeast Artificial Chromosome Libraries
for Screening with Unique Sequences, 296

Bales, R.C.

Oak Ridge National Laboratory, Oak Ridge, TN
Mobility of Microorganisms in a Sandy Aquifer, 636
University of Arizona, Tucson, AZ
Transport of Subsurface Biocolloids in
Porous Media, 654

Balhorn, R.L.

Lawrence Livermore National Laboratory,
Livermore, CA
Chromatin Structure in Mammalian Sperm, 126
DNA/Scanning Tunneling Microscopy, 433
X-Ray Holography, 434

Balkwill, D.L.

Florida State University, Tallahassee, FL
Establishment and Maintenance of a Subsurface
Microbial Culture Collection, 662
Phylogenetic Diversity Analysis of Deep Subsurface
Micro-Organisms, 661

Banda, M.

University of California, San Francisco,
San Francisco, CA
Biochemical Functions of Macrophages in
Pulmonary Damage from Environmental
Pollutants, 121

Barchet, W.R.

Pacific Northwest Laboratory, Richland, WA
DOE Atmospheric Chemistry Program
Management, 554
North Atlantic Regional Experiment Field
Campaign, 535

Barker, D.L.

Molecular Dynamics, Sunnyvale, CA
Rapid, High Throughput DNA Sequencing Using
Confocal Fluorescence Imaging of Capillary
Arrays, 379

Barnes, F.

Los Alamos National Laboratory, Los Alamos, NM
Remote Sensing of Surface Fluxes Important
to Cloud Development, 783

Barnes, F.J.

Los Alamos National Laboratory, Los Alamos, NM
Los Alamos National Environmental Research
Park, 696

Barnett, T.

Scripps Institution of Oceanography, La Jolla, CA
Atmospheric Radiation Measurement Tropical
Pacific Experiment: Role of Cloud, Water Vapor
and Convection Feedbacks in the Coupled Ocean/
Atmosphere System, 816

Barnett, T.P.

Scripps Institution of Oceanography, La Jolla, CA
Studies of Ocean Predictability at Decade to Century
Time Scales Using a Global Ocean General
Circulation Model in a Parallel Computing
Environment, 770

Barrio, J.R.

University of California, Laboratory of Biomedical
and Environmental Sciences, Los Angeles, CA
Nuclear Medicine Applications: Chemistry/
Biochemistry, 491

Barth, R.E.

Ohio State University, Columbus, OH
Synthesis and Evaluation of Boron Compounds
for Neutron Capture Therapy of Malignant
Brain Tumors, 519

Bartz, R.

Sea Tech, Inc., Corvallis, OR
Calibration of In Situ Optical Devices Using a Pure
Water Standard, 600
Development of a Spectral Attenuation Meter and a
Spectral Back Scattering Meter, 601

Bauer, J.

Florida State University, Tallahassee, FL
Transformation Rates and Fate of Dissolved, Colloidal,
and Particulate Forms of Organic Carbon in Ocean
Margins, 583

Baumgardner, J.R.

Los Alamos National Laboratory, Los Alamos, NM
Comparison of Methods for Solving the Spherical
Shallow Water Equations on the Connection
Machine, 732

Bazzaz, F.A.

Harvard University, Cambridge, MA
Integration of Experimental and Modeling Approaches
to Study Competitive Interactions Among Plants
Under Elevated CO₂, 840

Bechtold, W.E.

Inhalation Toxicology Research Institute,
Albuquerque, NM
Influence of Modifying Factors on Metabolic Fate of
Inhaled Organic Compounds, 17

Beck, R.N.

University of Chicago, Chicago, IL
Instrumentation and Quantitative Methods of
Evaluation, 499

Beeson, D.

University of California, Berkeley, Berkeley, CA
Pathways to Genetic Screening: Patient Knowledge
Patient Practices, 344

Bellinsky, S.A.

Inhalation Toxicology Research Institute,
Albuquerque, NM
Mechanisms of Chemically Induced
Carcinogenicity, 18

Bender, M.A.

Brookhaven National Laboratory, Upton, NY
DNA Repair, Cytogenetics, and Epidemiology, 14

Benner, W.H.

Lawrence Berkeley Laboratory, Berkeley, CA
Advanced Detectors for Mass Spectroscopy, 277

Benninger, L.K.

University of North Carolina at Chapel Hill,
Chapel Hill, NC
Carbon Cycling on the Continental Margin: Evidence
from Sediment ¹⁴C and Nutrient Elements, 594

Benson, S.M.

Lawrence Berkeley Laboratory, Berkeley, CA
An Interdisciplinary Approach to Spatial
Characterization of Contaminant Transport, 624

Berg, C.M.

University of Connecticut, Storrs, CT
A Probe-Based Mapping Strategy for DNA
Sequencing with Mobile Primers, 362

- Berkowitz, C.M.**
Pacific Northwest Laboratory, Richland, WA
Continental and Oceanic Fate/Air Pollutants, 556
- Berns, M.W.**
University of California, Irvine, Irvine, CA
A Center for Excellence for the Medical Application of Lasers, 490
- Beugelsdijk, T.J.**
Los Alamos National Laboratory, Los Alamos, NM
Automated Methods for Large Scale Physical Mapping, 312
- Bhattacharyya, M.H.**
Argonne National Laboratory, Argonne, IL
Biochemical Mechanisms of Chemically Induced Health Effects, 1
- Bice, D.E.**
Inhalation Toxicology Research Institute, Albuquerque, NM
Role of Immune Responses in Respiratory Diseases, 19
- Bigbee, W.L.**
Lawrence Livermore National Laboratory, Livermore, CA
Molecular Mechanisms of Mutagenesis: An In Vitro Glycophorin A-Based Cellular Model, 127
- Birdeall, T.**
Scripps Institution of Oceanography, La Jolla, CA
Acoustic Global Warming Feasibility Experiment, 865
- Birren, B.**
California Institute of Technology, Pasadena, CA
Developing a Physical Map of Human Chromosome 22 Using Pulse Alternating Current Electrophoresis and Large Fragment Cloning, 348
- Bishop, C.W.**
Idaho National Engineering Laboratory, Idaho Falls, ID
Hydrogeologic and Geochemical Controls on Micro-Organisms in Subsurface Formations, 619
- Bissell, M.J.**
Lawrence Berkeley Laboratory, Berkeley, CA
Molecular Carcinogenesis: Molecular Mechanisms Underlying Tissue-Specific Gene Expression, 122
- Biswas, P.K.**
Tuskegee Institute, Tuskegee, AL
Effects of Enriched CO₂, Water, and Nutrient Stress on Sweet Potatoes: Towards the Development of a Universal Crop Simulation Model, 852
- Blakely, E.A.**
Lawrence Berkeley Laboratory, Berkeley, CA
Clinical Heavy Ion Radiobiology, 461
Molecular Mechanism of Cell Effect: Molecular and Cellular Effects of Ionizing Radiations, 38
- Blaylock, B.G.**
Oak Ridge National Laboratory, Oak Ridge, TN
Radionuclides in the Environment, 630
- Blue, T.E.**
Ohio State University Research Foundation, Columbus, OH
An Accelerator Neutron Source for Boron Neutron Capture Therapy, 520
- Boecker, B.B.**
Inhalation Toxicology Research Institute, Albuquerque, NM
Toxicity of Injected Actinides, 20
- Bogen, D.**
Environmental Measurements Laboratory, New York, NY
Analytical Development, 211
Natural Radioactivity in the Biosphere, 210
- Bolch, W.E.**
Texas A&M University, College Station, TX
Considerations of Beta and Electron Transport in Internal Dose Calculations, 530
- Bolton, Jr., H.**
Pacific Northwest Laboratory, Richland, WA
Chemistry/Microbiology Controlling Chelated Radionuclide Transport, 648
Microbial Sequestration and Bioaccumulation of Radionuclides and Metals, 647
- Bond, V.P.**
Brookhaven National Laboratory, Upton, NY
Radiation Carcinogenesis Dose-Effect Relationships of Varying Energies of Neutrons in Leukemogenesis, 13
- Boothman, B.A.**
University of Michigan, Ann Arbor, MI
Role of X-Ray-Induced Transcripts in Adaptive Survival Responses Following X Rays, 92
- Borak, T.B.**
Colorado State University, Fort Collins, CO
Effects of Vegetation on Radon Transport Processes in Soil, 657
- Bossert, J.**
Los Alamos National Laboratory, Los Alamos, NM
Terrain-Influenced Meteorology, 551
- Bouma, III, H.**
Baylor College of Medicine, Institute of Religion, Houston, TX
National Study Conference on Genetics, Religion, and Ethics, 334
- Boyd, J.B.**
University of California, Davis, Davis, CA
Studies of the Repair of Radiation-Induced Genetic Damage in *Drosophila*, 156

Boyd, S.A.

Michigan State University, East Lansing, MI
Physicochemical and Microbiological Factors
Influencing the Bioavailability of Organic
Contaminants in Subsoils, 669

Boyle, W.R.

Oak Ridge Institute for Sciences and Education,
Oak Ridge, TN
Technical Assistance for Committee on Interagency
Radiation Research and Policy Coordination, 51

Braby, L.A.

Pacific Northwest Laboratory, Richland, WA
Biological Effectiveness of Radon Alpha
Particles, 231
Radiation Dosimetry, 191

Bradbury, E.M.

Los Alamos National Laboratory, Los Alamos, NM
Control of Cell Cycle and Transformation, 133
University of California, Davis, Davis, CA
Neutron Scatter Studies of Chromatin, 440

Bradley, R.S.

University of Massachusetts, Amherst, MA
Climate System Research: Studies of Global
and Regional Instrument Data, 755

Brandriff, B.F.

Lawrence Livermore National Laboratory,
Livermore, CA
DNA Sequence Mapping by Fluorescence In Situ
Hybridization, 293
Human Sperm Chromatin and Chromosomes, 43

Branscomb, E.W.

Lawrence Livermore National Laboratory,
Livermore, CA
Computational Support for the Human Genome
Center: Statistical and Mathematical Analysis,
Data Processing, and Databasing, 286

Brennan, T.M.

Lawrence Berkeley Laboratory, Berkeley, CA
Sequencing by Hybridization, 273

Briggs, P.

U.S. Geological Survey, Denver, CO
Geohydrologic, Geologic, and Geochemical
Processes Affecting Radon-222 in Groundwaters
from Crystalline-Rock Aquifers, 685

Brockman, F.J.

Pacific Northwest Laboratory, Richland, WA
Chemical Remediation Concepts: Bioremediation
Concepts, 644

Broecker, W.S.

Columbia University, Palisades, NY
Steady-State and Transient Modeling of Tracer and
Nutrient Distributions in the Global Ocean, 858

The Effects of Changing Land Use on Carbon and
Nitrogen in Mid-Latitude North American Soil
and Rice Paddies, 836

Bronstein, I.

Tropix, Inc., Bedford, MA
Development of Chemiluminescence-Based DNA
Sequencing Kits and Systems, 396

Brooks, A.L.

Pacific Northwest Laboratory, Richland, WA
Genotoxicity of Inhaled Energy Effluents, 66
In Vivo/In Vitro Radon-Induced Cellular Damage, 67
Low-Level $^{239}\text{PuO}_2$ Lifespan Studies, 65

Brooks, M.H.

Brookhaven National Laboratory, Upton, NY
Brookhaven Medical Research Reactor Operations, 459

Brown, G.M.

Oak Ridge National Laboratory, Oak Ridge, TN
Detection of Luminescence from Lanthanide Ions
as Labels for DNA Sequencing, 314
DNA Sequencing Using Stable Isotopes, 317
Using Scanning Tunneling Microscopy to Sequence
the Human Genome, 315

Brown, S.

Columbia University, New York, NY
Chromosome Specific cDNAs and Sequence-Tagged
Sites, 357

Brown, S.

University of Illinois, Urbana, IL
Spatial and Temporal Patterns of Biotic Exchanges
of CO_2 Between the Atmosphere and Tropical
Landscapes and Their Role in the Global
Carbon Balance, 841

Brownell, G.L.

Massachusetts General Hospital, Boston, MA
High Resolution Tomographic Instrument
Development, 509

Broyde, S.

New York University, New York, NY
Molecular Understanding of Mutagenicity Using
Potential Energy Methods, 173

Bruce, D.

Los Alamos National Laboratory, Los Alamos, NM
Pooling Yeast Artificial Chromosome Libraries
for Screening with Unique Sequences, 296

Brugger, R.M.

Brookhaven National Laboratory, Upton, NY
Joint Proposal for Neutron Capture Therapy, 448

Bruno, W.

Los Alamos National Laboratory, Los Alamos, NM
Pooling Yeast Artificial Chromosome Libraries for
Screening with Unique Sequences, 296

Bruno, D.

Idaho National Engineering Laboratory, Idaho Falls, ID
Planning Guide to Long-Term Ecological
Monitoring for Global Change at DOE
Research Parks, 694

Buchanan, M.V.

Oak Ridge National Laboratory, Oak Ridge, TN
Isomers and Interactables: Identification of
Bio-Adducts, 223

Buckner, M.A.

Oak Ridge National Laboratory, Oak Ridge, TN
Radiation Calibration Laboratory, 227

Budinger, T.F.

Lawrence Berkeley Laboratory, Berkeley, CA
Development of Radionuclides for Medical
Imaging Purposes, 464
Human Brain and Heart Metabolism and
Flow Measurements by Noninvasive
Techniques, 465

Bulger, R.E.

National Academy of Sciences Institute of Medicine,
Washington, DC
Predicting Future Disease: Issues in the
Development, Application, and Use of
Tests for Genetic Disorders, 381

Bunick, G.J.

Oak Ridge National Laboratory, Oak Ridge, TN
Structural Biology of Nucleosomes, 436

Buonocore, E.

University of Tennessee, Knoxville, TN
Consortium to Develop Medical Uses of Nuclear
Magnetic Resonance Imaging, 527

Burke, C.

Los Alamos National Laboratory, Los Alamos, NM
Construction of Restriction Maps Using Simulated
and Real Data, 310

Burlage, R.S.

Oak Ridge National Laboratory, Oak Ridge, TN
Mobility of Microorganisms in a Sandy Aquifer, 636

Bushaw, B.A.

Pacific Northwest Laboratory, Richland, WA
Determination of Radon Exposure: Laser
Measurements of ^{210}Pb , 230

Busness, K.M.

Pacific Northwest Laboratory, Richland, WA
Research Aircraft Operations, 557

Byrne, R.N.

Science Applications International Corp., San Diego, CA
Evaluation of a New General Circulation
Model-Capable Stochastic Cloud/Radiation
Parameterization Using Atmospheric
Radiation Measurement Data, 815

Callahan, A.P.

Oak Ridge National Laboratory, Oak Ridge, TN
Biomedical Radioisotope Technology
Development, 479
Nuclear Medicine and Biomedical Radioisotope
Technology, 478

Calloott, T.A.

Oak Ridge National Laboratory, Oak Ridge, TN
Physics of Solids and Macromolecules, 182

Callen, D.F.

Los Alamos National Laboratory, Life Sciences Division,
Los Alamos, NM
Construction of a 1.6 Megabase Average
Resolution Sequence-Tagged Site Map of
Human Chromosome 16, 297
Los Alamos National Laboratory, Los Alamos, NM
Construction of a Cosmid, Yeast Artificial
Chromosome, and Sequence-Tagged Site
Physical Map of Human Chromosome 16, 299

Campbell, E.W.

Los Alamos National Laboratory, Los Alamos, NM
Construction and Characterization of Human
Genomic Yeast Artificial Chromosome Library
with a Low Frequency of Chimeric Clones, 308
High Precision Mapping of Yeast Artificial
Chromosome Clones onto Chromosome 21 by
Fluorescence In Situ Hybridization and Image
Analysis, 304

Cantor, C.R.

Boston University, Boston, MA
Overcoming Genome-Mapping Bottlenecks, 340

Capel, M.S.

Brookhaven National Laboratory, Upton, NY
Synchrotron X-Radiation Scattering Spectrometer
for the Study of Biological Structures, 411

Carman, Jr., H.S.

Oak Ridge National Laboratory, Oak Ridge, TN
Chemical Physics Studies in the Gaseous and Liquid
Phases, 186
Ion Chemistry and Molecular Clustering
Phenomena, 189

Carnes, B.A.

Argonne National Laboratory, Argonne, IL
Interspecies Extrapolation for Radiation-Induced
Carcinogenic Risk, 2

Carrano, A.V.

Lawrence Livermore National Laboratory,
Livermore, CA
Assembly, Closure, and Characterization of a
Chromosome 19 Contig Map, 292
Coding Region Isolation, Mapping, and
Characterization, 290
Core Facility, 287
Human Genome Center, 285

- Interdigitation of the Physical and Generic Maps of Human Chromosome 19, 291
- Carroll, J.**
Geotech Inc., Grand Junction, CO
Extension of ^{210}Pb Geochronology with Inverse Numerical Techniques, 585
- Carter, J.G.**
Oak Ridge National Laboratory, Oak Ridge, TN
Electron-Molecule Interactions, 185
- Casey, D.K.**
Oak Ridge National Laboratory, Oak Ridge, TN
Human Genome Management Information System, 322
- Caskey, C.T.**
Baylor College of Medicine, Houston, TX
Mapping and Ordered Cloning of the Human X Chromosome, 336
National Study Conference on Genetics, Religion, and Ethics, 334
- Cassett, J.**
National Institutes of Health, Bethesda, MD
GenBank: The Genetic Sequence Data Bank, 382
- Casson, W.H.**
Oak Ridge National Laboratory, Oak Ridge, TN
Radiation Calibration Laboratory, 227
- Castleman, Jr., A.W.**
Pennsylvania State University, University Park, PA
Clusters: Elucidating the Dynamics of Ionization Events and Ensuing Reactions in the Condensed Phase, 205
Radon: Chemical and Physical Processes Associated with Its Distribution and Effects, 248
- Castro, J.R.**
Lawrence Berkeley Laboratory, Berkeley, CA
Clinical Heavy Ion Radiobiology, 461
- Caswell, R.S.**
National Institute of Standards and Technology, Gaithersburg, MD
Neutron Interactions with Biological Tissue, 201
Radon: Energy Deposition and Radiation Quality of Radon and Radon Daughters, 244
- Caton, G.M.**
Oak Ridge National Laboratory, Oak Ridge, TN
Radon Information Transfer, 64
- Cavalli-Sforza, L.C.**
Stanford University, Stanford, CA
Human Genetic Diversity, 394
- Cerni, T.A.**
K.C. Research Corporation, Littleton, CO
A Marine Boundary Layer Water Vapor Flux Sensor, 586
- Cess, R.D.**
State University of New York at Stony Brook, Stony Brook, NY
Carbon Dioxide-Induced Climate Change, 772
- Chait, B.**
University of Wisconsin, Madison, WI
High Speed DNA Sequence Analysis by Matrix-Assisted Laser Desorption Mass Spectrometry, 404
- Chang, E.**
Dynamics Technology, Inc., Torrance, CA
Development of a Moored Optical Instrument for Measurement of Oceanic Particle Size and Settling Rate, 582
- Chapin, III, F.S.**
University of California, Berkeley, Berkeley, CA
Controls Over Nutrients Flow Through Plants and Microbes in Arctic Tundra, 710
- Chatterjee, A.**
Lawrence Berkeley Laboratory, Berkeley, CA
Diagnostic Use of High Energy Radioactive Beams in Cancer Therapy and Nuclear Medicine, 462
Radiological Physics and Chemistry: Mechanistic Theoretical Models for Radiation-Induced Mutation and Transformation, 180
- Chedd, G.**
WGBH Educational Foundation, Boston, MA
The Secret of Life, 402
- Chen, C.H.**
Oak Ridge National Laboratory, Oak Ridge, TN
Chemical Kinetics of Irradiated Materials, 183
Resonance Ionization Spectroscopy, 225
Vacuum Ultraviolet Ionizer Mass Spectrometer for Genome Sequencing, 321
- Chen, D.J.**
Los Alamos National Laboratory, Los Alamos, NM
Molecular Genetics of Radiation Repair Genes, 134
Molecular Mechanisms of Radiation-Induced Mutations, 46
Regulate Mammalian Cell Cycle Progression, 48
- Chen, E.**
California Institute of Technology, Pasadena, CA
Biological Information Signal Processor: Very Large Scale Integration Solutions to Sequence Comparison Problems, 349
- Cheng, J.**
Lawrence Berkeley Laboratory, Berkeley, CA
Human Genome Center/Isolation of Chromosome 21 cDNA Clones, 267
Human Genome Center/Rapid Isolation and Organization of Chromosome 21 YAC Clones, 269

- Human Genome Center/Rapid Isolation and Organization of Chromosome 21 YAC Clones**, 268
- Cheng, Y.S.**
Inhalation Toxicology Research Institute, Albuquerque, NM
 Dynamics of Radon Daughter Interactions with Indoor Aerosols, 218
- Chervin, R.M.**
National Center for Atmospheric Research, Boulder, CO
 Scientific Development of a Massively Parallel Ocean Climate Model, 759
- Chipman, D.W.**
Columbia University, Palisades, NY
 Development of Gas Chromatographic System for Dissolved Organic Carbon Analysis in Seawater, 581
- Christophorou, L.G.**
Oak Ridge National Laboratory, Oak Ridge, TN
 Atomic, Molecular, and Interphase Physics, 184
 Electron-Molecule Interactions, 185
- Chugani, D.C.**
University of California, Laboratory of Biomedical and Environmental Sciences, Los Angeles, CA
 Nuclear Medicine Applications: Molecular and Cellular Biology, 492
- Church, G.M.**
Harvard Medical School, Boston, MA
 Developing a Fully Integrated Technology for Sequencing Genomes as Large as Those of Humans, 368
- Churchill, J.H.**
Woods Hole Oceanographic Institution, Woods Hole, MA
 A Study of Sediment Motion and Bottom Boundary Layer Dynamics Over the Middle Atlantic Bight Shelf and Upper Slope, 612
- Churchman, D.L.**
University of Delaware, Lewes, DE
 The Effect of Bacteria and Microbial Metabolites on Mineral Dissolution in Subsurface Environments, 659
- Cinkosky, M.**
Los Alamos National Laboratory, Los Alamos, NM
 Construction of a Cosmid, Yeast Artificial Chromosome, and Sequence-Tagged Site Physical Map of Human Chromosome 16, 299
- Cleaver, J.E.**
University of California, San Francisco, San Francisco, CA
 DNA Replication and Repair, 119
- Mammalian Cell Culture Systems for Molecular Studies of DNA, Mutagenicity, and Carcinogenicity**, 118
- Mechanisms of Mutagenesis by Alpha Particle and X Rays in Human Cells**, 15
- Clements, W.E.**
Los Alamos National Laboratory, Los Alamos, NM
 Remote Sensing of Surface Fluxes Important to Cloud Development, 783
 Terrain-Influenced Meteorology, 551
- Clifton, K.H.**
University of Wisconsin Clinical Cancer Center, Madison, WI
 Radiogenic Neoplasia in Thyroid and Mammary Clonogens, 107
- Coderre, J.A.**
Brookhaven National Laboratory, Upton, NY
 Clinical Feasibility of Boron Neutron Capture Therapy Using p-Boronophenylalanine, 449
- Cohen, B.S.**
New York University Medical Center, New York, NY
 Particle Deposition in Human and Canine Tracheobronchial Casts, 96
- Cole, D.A.**
Los Alamos National Laboratory, Los Alamos, NM
 Detection and Treatment of Lung Cancer Using $^{64}\text{CuTCPP}$, 471
 Imaging Agents for Lymph Nodes and Inflammatory Lesions, 470
- Collorelli, J.**
University of California, Laboratory of Biomedical and Environmental Sciences, Los Angeles, CA
 DNA Replication, Recombination and Repair, 158
- Collins, D.L.**
University of Kansas Medical Center, Kansas City, KS
 Human Genetics Education for Middle and Secondary Science Teachers, 373
- Colwell, F.S.**
Idaho National Engineering Laboratory, Idaho Falls, ID
 Complete Degradation of Mixed Halocarbons by Methanogenic and Methanotrophic Microbial Communities, 620
 Deep Subsurface Sample Analysis at Idaho National Engineering Laboratory, 621
 Drilling and Sampling Technology Research, 663
- Compton, R.N.**
Oak Ridge National Laboratory, Oak Ridge, TN
 Chemical Physics Studies in the Gaseous and Liquid Phases, 186
 Ion Chemistry and Molecular Clustering Phenomena, 189
 Nanosecond and Picosecond Nonlinear Laser Techniques, 226

Cook, J.S.

Oak Ridge National Laboratory, Oak Ridge, TN
Regulation of Membrane Transport, 143

Cooper, D.I.

Los Alamos National Laboratory, Los Alamos, NM
Application of a Solar-Blind LIDAR for
Atmospheric and Ecological Studies, 698

Cooper, M.

University of Chicago, Chicago, IL
Quantitative Studies in Radiopharmaceutical
Science, 500

Cortopassi, G.A.

University of Southern California, Los Angeles, CA
Direct Detection of Mutations in Human
Mitochondrial and Nuclear DNA Using
the Polymerase Chain Reaction, 100

Costrell, L.

National Institute of Standards and Technology,
Gaithersburg, MD
Instrumentation for Nuclear Applications, 245

Coughenour, M.B.

Colorado State University, Fort Collins, CO
Grassland/Atmospheric Response to Climate
Change: Coupling Regional and Local Scales, 713

Coulter, R.L.

Argonne National Laboratory, Argonne, IL
Area-Representative Estimates of Surface Heat Flux
for Clouds and Radiation Testbed Sites, 776
Atmospheric Boundary Layer Transport and
Dispersion Studies, 536

Cox, S.K.

Colorado State University, Fort Collins, CO
Monitoring the Response of the Upper Troposphere/
Lower Stratosphere to a Greenhouse Gas
Scenario, 800

Coyne, J.J.

National Institute of Standards and Technology,
Gaithersburg, MD
Neutron Interactions with Biological Tissue, 201

Cramer, S.P.

Lawrence Berkeley Laboratory, Berkeley, CA
Biological X-Ray Spectroscopy Resource Center, 431

Crandall, L.A.

Morehouse School of Medicine, Atlanta, GA
Impact of Technology Derived from the Human
Genome Project on Genetic Testing, Screening,
and Counseling: Cultural, Ethical, and Legal
Issues, 380

Crewe, A.V.

University of Chicago, Chicago, IL
Electron Microscope Development, 441

Cristy, M.

Oak Ridge National Laboratory, Oak Ridge, TN
Medical Physics and Internal Dosimetry, 224

Crkvenjakov, R.

Argonne National Laboratory, Argonne, IL
An Integral Approach to Genome Studies, 258

Cross, F.T.

Pacific Northwest Laboratories, Richland, WA
Mechanisms of Radon Injury, 69
Radon Hazards in Homes, 68

Crowley, T.J.

Applied Research Corporation, College Station, TX
Studies in Regional Climate Sensitivity,
Predictability, and Temporal Response, 738

Cushman, J.H.

Purdue Research Foundation, West Lafayette, IN
Supercomputer Simulation of Clay-Chemical-
Water Interactions: Phase III, 681

Cushman, R.

Oak Ridge National Laboratory, Oak Ridge, TN
Carbon Dioxide Information Analysis Center, 825
Carbon Dioxide Information and Analysis Research
Program: Resource Analysis, 826
Database Support to Assist in Quantifying the Link
Between Changes in Atmospheric Composition
and Climate Change, 788

D'Anna, J.A.

Los Alamos National Laboratory, Los Alamos, NM
Regulate Mammalian Cell Cycle Progression, 48

Dagg, M.

Louisiana Universities Marine Consortium,
Chauvin, LA
Assimilation and Transfer of Carbon in
Oligotrophic and Eutrophic Coastal Water
Columns, 587

Dahl, A.R.

Inhalation Toxicology Research Institute,
Albuquerque, NM
Influence of Respiratory Tract Metabolism on
Effective Dose, 21

Dalsey, J.M.

Lawrence Berkeley Laboratory, Berkeley, CA
Air Pollutant Exposures in Buildings, 36

Dannals, R.F.

The Johns Hopkins University School of Medicine,
Baltimore, MD
Synthesis of Tracers Using Automated
Radiochemistry and Robotics, 508

Dannevik, W.P.

Lawrence Livermore National Laboratory,
Livermore, CA
Climate Systems Modeling on Massively
Parallel Computers I: Global Ocean Circulation
Model, 722

Daum, P.H.

Brookhaven National Laboratory, Upton, NY
Analysis of Aerosol Chemical and Microphysical
Data in the North Atlantic Regional
Experiment, 542

Continental and Oceanic Fate of Energy-Related
Air Pollutants, 541

Radiative Properties of Nonuniform Clouds, 778

Davidovits, P.

Boston College, Chestnut Hill, MA
Measurement of Gas-Water Uptake Coefficients for
Trace Gases Active in the Marine
Environment, 563

Davidson, J.B.

Oak Ridge National Laboratory, Oak Ridge, TN
Genomic Instrumentation Development:
Detection Systems for Film and High Speed
Gel-Less Methods, 323

Davidson, K.A.

Oak Ridge National Laboratory, Oak Ridge, TN
Human Genome Management Information
System, 322

Day, W.

U.S. Geological Survey, Denver, CO
Geohydrologic, Geologic, and Geochemical
Processes Affecting Radon-222 in Groundwaters
from Crystalline-Rock Aquifers, 685

Deaven, L.L.

Los Alamos National Laboratory, Los Alamos, NM
Chromosome Structure and Function, 135

Construction and Characterization of Human
Genomic Yeast Artificial Chromosome Library
with a Low Frequency of Chimeric Clones, 308

Construction of a Cosmid, Yeast Artificial
Chromosome, and Sequence-Tagged Site
Physical Map of Human Chromosome 16, 299

High Precision Mapping of Yeast Artificial
Chromosome Clones onto Chromosome 21 by
Fluorescence In Situ Hybridization and Image
Analysis, 304

Human Recombinant DNA Library, 298

Systematic Generation of Chromosome 5 Specific
Sequence-Tagged Sites, 301

de Fatima Bonaldo, M.

Columbia University, New York, NY
Chromosome Specific cDNAs and
Sequence-Tagged Sites, 357

DeGrandpre, M.D.

Woods Hole Oceanographic Institution,
Woods Hole, MA

Fiber Optic Chemical Sensors for Characterizing
the Carbon Cycle in Ocean Margin Regions, 609

Dehmer, J.L.

Argonne National Laboratory, Argonne, IL
Highly Selective Probes of Molecular Photophysics
and Photochemistry, 208

Dehmer, P.M.

Argonne National Laboratory, Argonne, IL
Highly Selective Probes of Molecular Photophysics
and Photochemistry, 208

de Jong, P.J.

Lawrence Livermore National Laboratory,
Livermore, CA

Assembly, Closure, and Characterization of a
Chromosome 19 Contig Map, 292

National Laboratory Gene Library Project, 289
New Mapping Strategies, 288

Del Genio, A.D.

National Aeronautics and Space Administration,
New York, NY

Observational Analysis of Climate Feedbacks and
Trends, 808

Delmore, J.E.

Idaho National Engineering Laboratory, Idaho Falls, ID
Neutral Beam Microprobe, 217

DeLuca, P.M.

University of Wisconsin, Madison, WI
Fast Neutron Dosimetry, 256

Delwiche, C.C.

University of California, Davis, Davis, CA
National Institute for Global Environmental
Change, 869

DeNardo, S.J.

University of California, Davis, Sacramento, CA
Copper-67 Lym-1 Feasibility Trial of Therapy for
Lymphoma, 488

Denbo, D.W.

Pacific Northwest Laboratory, Sequim, WA
Ocean Convection Parameterization, 736

Denison, K.S.

Los Alamos National Laboratory, Los Alamos, NM
Sequencing and Mapping of cDNAs from a
Paternaly Encoded Human Pregnancy, 300

Denton, M.B.

University of Arizona, Tucson, AZ
Single-Molecule Detection Using Charge Coupled
Device Array Technology, 331

Derenzo, S.E.

Lawrence Berkeley Laboratory, Berkeley, CA
Improved Instrumentation for Positron
Tomography, 466

Dettloff, W.

Advanced Technology Applications, Inc., Research
Triangle Park, NC

Interactive DNA Sequence Processing for a
Microcomputer, 327

de Vella, J.

University of California, Laboratory of Biomedical
and Environmental Sciences, Los Angeles, CA
Developmental Neurotoxicology, 82

Dewey, S.

Brookhaven National Laboratory, Upton, NY
A Regional Cyclotron-Positron Emission
Tomography Center for Radiotracer Research
and Medical Application, 447

Dickinson, R.E.

University of Arizona, Tucson, AZ
The Land Component of the Global Climate
System with Adequate Spatial Resolution, 739

Dickson, A.G.

Scripps Institution of Oceanography, La Jolla, CA
The Quality Control of Oceanic Carbon Dioxide
Measurements: Preparation and Distribution of
Reference Materials, 862

Dietz, R.N.

Brookhaven National Laboratory, Upton, NY
Advancements in Atmospheric Tracers and
Related Instrumentation, 209
Atmospheric Tracer and Instrumentation
Development, 543

Dilmanian, F.A.

Brookhaven National Laboratory, Upton, NY
Multiple Energy Computed Tomography for
Neuroradiology with Monochromatic X Rays
from the National Synchrotron Light Source, 450

Dizdaroğlu, M.M.

National Institute of Standards and Technology,
Gaithersburg, MD
Ionizing Radiation-Induced DNA Damage and Its
Repair in Human Cells, 172

Doggett, N.A.

Los Alamos National Laboratory, Los Alamos, NM
Construction of a Cosmid, Yeast Artificial
Chromosome, and Sequence-Tagged Site
Physical Map of Human Chromosome 16, 299
Construction of Restriction Maps Using Simulated and
Real Data, 310
Pooling Yeast Artificial Chromosome Libraries for
Screening with Unique Sequences, 296

Doran, J.C.

Pacific Northwest Laboratory, Richland, WA
Atmospheric Studies in Complex Terrain Program:
Scientific Direction, 558
Direct Simulation of Atmospheric Turbulence, 559
Point-Area Relationships for Global Climate
Modeling, 791

Douhart, R.J.

Pacific Northwest Laboratory, Richland, WA
GnomeView: A Graphical Interface to the Human
Genome, 325

Dovlohl, N.J.

University of Alberta, Edmonton, Alberta T6G 2G2
Canada
Multicolumn Gel Electrophoresis and Laser-Induced
Fluorescence Detection for DNA Sequencing at
64,000 Bases/Hour, 329

Downing, J.P.

Pacific Northwest Laboratory, Sequim, WA
Carbon Dioxide Ocean Research, 857

Drake, B.G.

Smithsonian Institution, Edgewater, MD
A Field Study of the Effects of Elevated Ambient
CO₂ on Ecosystem Processes in Chesapeake
Bay Wetlands, 849

Drmanac, R.

Argonne National Laboratory, Argonne, IL
An Integral Approach to Genome Studies, 258

Druyan, L.M.

Columbia University, New York, NY
The Impact of Recent Model Improvements on
Goddard Institute for Space Studies General
Circulation Model Predictions of Climate
Change, 747

D'Silva, A.P.

Ames Laboratory, Ames, IA
Laser-Based Studies of DNA Damage and
Chemical Carcinogenesis, 207

Dubnick, M.

The Institute for Genomic Research, Gaithersburg, MD
Expressed Sequence Tags from Human Brain cDNAs
for Genome Mapping, 370

DuBois, R.D.

Pacific Northwest Laboratory, Richland, WA
Radiation Physics, 192

Dudney, C.S.

Oak Ridge National Laboratory, Oak Ridge, TN
Investigation of Radon Entry and Effectiveness of
Mitigation Measures, 639

Dunn, J.J.

Brookhaven National Laboratory, Upton, NY
Large Scale DNA Sequencing with a Primer
Library, 262
Nucleic Acid Replication, 111
Rapid Preparation of DNA for Automated
Sequencing, 260

Duster, T.

University of California, Berkeley, Berkeley, CA
Pathways to Genetic Screening: Patient Knowledge
Patient Practices, 344

Earle, C.W.

University of Arizona, Tucson, AZ
Single-Molecule Detection Using Charge Coupled
Device Array Technology, 331

Ebbe, S.N.

Lawrence Berkeley Laboratory, Berkeley, CA
Vascular and Blood Diseases, 467

Eckerman, K.F.

Oak Ridge National Laboratory, Oak Ridge, TN
Medical Physics and Internal Dosimetry, 224

Edmonds, C.G.

Pacific Northwest Laboratory, Richland, WA
Ion Cyclotron Resonance Mass Spectroscopy of
DNA Molecular Ions, 324

Edmonds, J.A.

Pacific Northwest Laboratory, Washington, DC
Energy and Future Carbon Dioxide Emissions, 829
Resource Analysis Research, 830

Efstratiadis, A.

Columbia University, New York, NY
Chromosome Specific cDNAs and
Sequence-Tagged Sites, 357

Ehleringer, J.R.

University of Utah, Salt Lake City, UT
Water Use, Productivity, and Interactions
Among Desert Plants: Vertical Integration
Using Stable Isotope Ratios, 718

Eichinger, W.E.

Los Alamos National Laboratory, Los Alamos, NM
Application of a Solar-Blind LIDAR for
Atmospheric and Ecological Studies, 698

Eldarov, M.

National Institute of Environmental Health Science,
Research Triangle Park, NC
Genetic Analysis of Yeast Artificial Chromosome
Following Yeast Transformation and Mitotic
Growth, 303

Eller, P.G.

Los Alamos National Laboratory, Los Alamos, NM
Co-Contaminant Reaction Chemistry at
Interfaces, 629

Ellingson, R.G.

University of Maryland, College Park, MD
Intercomparison of Radiation Codes in
Climate Models Phase II: Verification
and Calibration, 806

Emanuel, K.A.

Massachusetts Institute of Technology,
Cambridge, MA
Development of an Advanced Representation of
Cumulus Convection, 756

Emanuel, W.R.

Oak Ridge National Laboratory, Oak Ridge, TN
Carbon Cycle Program Management, 827

Entzminger, J.N.

Defense Advanced Research Projects Agency,
Arlington, VA
A JASON Study of Selected Topics for DOE, 802

Eposito, M.S.

Lawrence Berkeley Laboratory, Berkeley, CA
Mitotic Recombination and DNA Repair, 123

Evans, G.A.

The Salk Institute for Biological Studies, La Jolla, CA
Technology Development for Physical Mapping of
Human Chromosomes, 393

Evans, H.H.

Case Western Reserve University, Cleveland, OH
Mutagenicity of Radon and Radon Daughters, 86

Everett, K.R.

Ohio State University Research Foundation,
Columbus, OH
Hydrological and Geochemical Response and
Recovery in Disturbed Arctic Ecosystems, 715

Fabrikant, J.I.

Lawrence Berkeley Laboratory, Berkeley, CA
Effects of Heavy Particle Radiation, 468
Heavy Ion Radiosurgery, 469

Falkowski, P.G.

Brookhaven National Laboratory, Upton, NY
Coastal Productivity, 573
Diagnostic Analysis of Iron Limitation of CO₂
Uptake by Oceanic Phytoplankton, 854
Molecular Ecology of Phytoplankton
Photosynthesis, 574

Fasham, Jr., M.

National Environment Research Council, Surrey
GUS SUB United Kingdom
Simulations of the Carbon Cycle in the
Oceans, 844

Feltshane, I.

Columbia University Law School, New York, NY
Lawful Uses of Knowledge from the Human Genome
Project, 358

Ferrell, T.L.

Oak Ridge National Laboratory, Oak Ridge, TN
Liquid and Submicron Physics, 187
Using Scanning Tunneling Microscopy to Sequence
the Human Genome, 315

Ferrieri, R.F.

Brookhaven National Laboratory, Upton, NY
A Regional Cyclotron-Positron Emission
Tomography Center for Radiotracer Research
and Medical Application, 447

Floken, J.W.

Los Alamos National Laboratory, Los Alamos, NM
Construction of a Cosmid, Yeast Artificial
Chromosome, and Sequence-Tagged Site
Physical Map of Human Chromosome 16, 299

Fields, C.A.

The Institute for Genomic Research,
Gaithersburg, MD
Expressed Sequence Tags from Human Brain
cDNAs for Genome Mapping, 370
Identification of Genes in Anonymous DNA
Sequences, 369

Finch, G.L.

Inhalation Toxicology Research Institute,
Albuquerque, NM
Mechanisms of Granulomatous Disease from
Inhaled Beryllium, 22

Fish, W.

Oregon Graduate Center, Beaverton, OR
Adsorption of Chromate/Organic Acid Waste
Mixtures in Aquifer Materials, 677

Fisk, W.J.

Lawrence Berkeley Laboratory, Berkeley, CA
Experimental and Theoretical Investigations of
Radon Availability, Migration, and Entry, 623

Flagg, C.N.

Brookhaven National Laboratory, Upton, NY
Coastal Transport and Diffusion, 575

Flynn, E.R.

Los Alamos National Laboratory, Los Alamos, NM
Imaging Function in the Human Brain, 474

Fodor, S.P.A.

Affymax Research Institute, Palo Alto, CA
Spatially Defined Oligonucleotide Arrays, 328

Folger, P.

U.S. Geological Survey, Denver, CO
Geohydrologic, Geologic, and Geochemical
Processes Affecting Radon-222 in Groundwaters
from Crystalline-Rock Aquifers, 685

Foots, R.S.

Oak Ridge National Laboratory, Oak Ridge, TN
Detection of Luminescence from Lanthanide Ions
as Labels for DNA Sequencing, 314
DNA Sequence Analysis by Solid-Phase
Hybridization, 316
DNA Sequencing Using Stable Isotopes, 317
Genomic Instrumentation Development: Detection
Systems for Film and High Speed Gel-Less
Methods, 323
Protein Engineering and Molecular Mutagenesis, 146

Ford, A.

Los Alamos National Laboratory, Los Alamos, NM
Pooling Yeast Artificial Chromosome Libraries for
Screening with Unique Sequences, 296

Foster, I.T.

Argonne National Laboratory, Argonne, IL
Parallel Atmospheric Climate Model, 720

Fowler, J.S.

Brookhaven National Laboratory, Upton, NY
A Regional Cyclotron-Positron Emission
Tomography Center for Radiotracer Research
and Medical Application, 447

Francis, A.J.

Brookhaven National Laboratory, Upton, NY
Biodegradation of Selected Organic Compounds
and Complexing Agents of Radionuclides and
Metals, 616
Role of Micro-Organisms as Regulators of
Uranium Mobility in Natural Radioactive
Mineral Deposits, 617

Francomano, C.

The Johns Hopkins University School of Medicine,
Baltimore, MD
A Human Genome Database, 372

Frank, M.L.

Oak Ridge National Laboratory, Oak Ridge, TN
Radionuclides in the Environment, 630

Fredrickson, J.F.

Pacific Northwest Laboratory, Richland, WA
Subsurface Microbial Phenomena, 640

Fredrickson, J.K.

Pacific Northwest Laboratory, Richland, WA
Deep Subsurface Microbiological
Investigations, 641

Frishman, D.

U.S. Geological Survey, Denver, CO
Geohydrologic, Geologic, and Geochemical
Processes Affecting Radon-222 in Groundwaters
from Crystalline-Rock Aquifers, 685

Fritz, T.E.

Argonne National Laboratory, Argonne, IL
Radiation Toxicity Studies in Dogs for Interspecies
Comparison, 3

Frome, E.L.

Oak Ridge National Laboratory, Oak Ridge, TN
Biostatistics and Biomathematics, 63

Fruchter, J.S.

Pacific Northwest Laboratory, Richland, WA
Manipulation of Natural Subsurface Processes:
Field Research and Validation, 645

Fry, B.

Marine Biological Laboratory, Woods Hole, MA
Origins and Fates of Dissolved Organic
Matter Along the New England
Continental Margin, 589

Fuolarelli, A.F.

Pacific Northwest Laboratory, Richland, WA
Biochemistry of Free Radical-Induced DNA
Damage, 70

- Fulco, A.J.**
University of California, Laboratory of Biomedical and Environmental Sciences, Los Angeles, CA
Biosynthetic Control, 159
- Fung, I.Y.-S.**
National Aeronautics and Space Administration, New York, NY
Spatial and Temporal Patterns of Biotic Exchanges of CO₂ Between the Atmosphere and Tropical Landscapes and Their Role in the Global Carbon Balance, 843
- Gabra, N.**
Massachusetts Institute of Technology, Cambridge, MA
Robust Detailed Mapping of the Human Genome, 377
- Gadgil, A.J.**
Lawrence Berkeley Laboratory, Berkeley, CA
Characterization of Airborne Radon Concentrations, 219
- Gaffney, J.S.**
Argonne National Laboratory, Argonne, IL
Atmospheric Chemistry of Organic Oxidants and Aldehydes, 537
Investigation of Organic/Inorganic Complexation Processes in Subsurface Environments, 615
Mechanisms of Colloidal Transport in Groundwater Environments, 614
- Gammage, R.B.**
Oak Ridge National Laboratory, Oak Ridge, TN
Dosimetry for New Energy Systems Pollutants, 229
Investigation of Radon Entry and Effectiveness of Mitigation Measures, 639
- Garbo, C.P.**
University of Arizona, Tucson, AZ
Transport of Subsurface Biocolloids in Porous Media, 654
- Garola, E.**
Lawrence Livermore National Laboratory, Livermore, CA
Assembly, Closure, and Characterization of a Chromosome 19 Contig Map, 292
Core Facility, 287
- Gardner, R.H.**
Oak Ridge National Laboratory, Oak Ridge, TN
System Processes in Landscape Ecology, 699
- Garrett, W.R.**
Oak Ridge National Laboratory, Oak Ridge, TN
Chemical Kinetics of Irradiated Materials, 183
Resonance Ionization Spectroscopy, 225
- Garten, C.T.**
Oak Ridge National Laboratory, Oak Ridge, TN
Walker Branch Watershed Project, 700
- Gates, W.L.**
Lawrence Livermore National Laboratory, Livermore, CA
Climate Model Diagnosis and Intercomparison, 723
Cray Computer, 724
- Gatewood, J.M.**
Los Alamos National Laboratory, Los Alamos, NM
A Loosely Coupled, Distributed Laboratory Notebook for the cDNA Community, 309
Sequencing and Mapping of cDNAs from a Paternally Encoded Human Pregnancy, 300
- Gatley, J.S.**
Brookhaven National Laboratory, Upton, NY
A Regional Cyclotron-Positron Emission Tomography Center for Radiotracer Research and Medical Application, 447
- Gatti, R.A.**
University of California, Los Angeles, Los Angeles, CA
Genetic Localization of Ataxia Telangiectasia Gene(s): A Human Gene(s) for Radiation Sensitivity, 163
- Geacintov, N.E.**
New York University, New York, NY
Base Sequence Effects on Interactions Between Aromatic Mutagens and DNA, 174
Mechanisms of Interaction of Radiation with Matter, 204
- Gee, G.W.**
Pacific Northwest Laboratory, Richland, WA
Radon Transport Modeling in Soils, 643
- Generoso, E.**
Oak Ridge National Laboratory, Oak Ridge, TN
Generating a Comparative Physical Map of Mouse Chromosome 7, 319
- Generoso, W.M.**
Oak Ridge National Laboratory, Oak Ridge, TN
Mammalian Chemical Mutagenesis Program, 55
Effects and Uses of Chromosome Aberrations, 144
Mammalian Genetics, 57
- Gesteland, R.F.**
University of Utah, Salt Lake City, UT
Advanced Sequencing Technology, 399
- Ghan, S.J.**
Pacific Northwest Laboratory, Richland, WA
Development of a General Circulation Model Stratiform Cloud Parameterization, 794
- Ghiorso, W.C.**
Cornell University, Ithaca, NY
Comparison of Distribution, Abundance, and Activities of Deep Subsurface Micro-Organisms at DOE Sites, 653
- Giddings, J.C.**
University of Utah, Salt Lake City, UT
Field-Flow Fractionation of Chromosomes, 398

- Giese, R.W.**
Northeastern University, Boston, MA
New Fluorescence Methodology for Detecting DNA Adducts, 247
- Gingrich, J.C.**
Lawrence Berkeley Laboratory, Berkeley, CA
Human Genome Center/ Chromosome 21 Physical Mapping, 270
- Glometti, C.S.**
Argonne National Laboratory, Argonne, IL
Analysis of Protein Expression, 4
- Girvin, D.C.**
Pacific Northwest Laboratory, Richland, WA
Chemistry/Microbiology Controlling Chelated Radionuclide Transport, 648
- Glazer, A.N.**
University of California, Berkeley, Berkeley, CA
Ultrasensitive Fluorescence Detection of DNA, 342
- Gold, L.S.**
Lawrence Berkeley Laboratory, Berkeley, CA
Risk Assessment in Carcinogenesis, 39
- Goldstein, N.**
Spectral Sciences, Inc., Burlington, MA
A Diode-Laser Absorption Remote Concentration Sensor, 255
A Diode-Laser Absorption Remote Concentration Sensor, 570
- Goodwin, E.H.**
Los Alamos National Laboratory, Los Alamos, NM
Chromosome Damage in the 1 Rad Region, 47
Strand-Specific Orientation of Satellite DNA Sequences Determined by Fluorescence In Situ Hybridization, 305
- Goyet, C.**
Woods Hole Oceanographic Institution, Woods Hole, MA
CO₂ Measurements Along the World Ocean Circulation Experiment P-16 and 19 Sections in the South Pacific Ocean: A Joint Lamont-Dougherty Geological Observatory/Woods Hole Oceanographic Institution Program, 868
- Grad, F.**
Columbia University Law School, New York, NY
Lawful Uses of Knowledge from the Human Genome Project, 358
- Grady, D.L.**
Los Alamos National Laboratory, Los Alamos, NM
Human Recombinant DNA Library, 298
Systematic Generation of Chromosome 5 Specific Sequence-Tagged Sites, 301
- Gray, H.**
Southern Methodist University, Dallas, TX
Statistical Examination of Climatological Data Relevant to Global Temperature Variations, 817
- Gray, J.**
University of California, San Francisco, San Francisco, CA
Molecular Cytogenetics and Computer-Assisted Microscopy, 346
- Grdina, D.J.**
Argonne National Laboratory, Argonne, IL
Mutagenesis and Carcinogenesis by Low Dose Irradiation, 5
- Grebmeier, J.M.**
Oak Ridge National Laboratory, Oak Ridge, TN
Radionuclides in the Coastal Zone, 702
- Greener, P.**
California Institute for Biological Research, La Jolla, CA
New Hosts and Vectors for Genome Cloning, 347
- Griffin, G.D.**
Oak Ridge National Laboratory, Oak Ridge, TN
Dosimetry for New Energy Systems Pollutants, 229
- Grossman, L.**
The Johns Hopkins University, Baltimore, MD
Role of DNA Damage and Repair in Chronic Disease, 167
- Gruner, S.M.**
Princeton University, Princeton, NJ
Development and Applications of Photo-Sensitive Device Systems to Studies of Biological and Organic Materials, 442
- Gschwend, P.P.**
Massachusetts Institute of Technology, Cambridge, MA
Colloids in Groundwater: Their Mobilization, Subsurface Transport, and Sorption Affinity for Toxic Chemicals, 667
- Guokert, J.B.**
University of Tennessee, Knoxville, TN
Biochemical Markers for In Situ Microbial Community Structure, 684
- Gudiksen, P.H.**
Lawrence Livermore National Laboratory, Livermore, CA
Complex Terrain Studies, 548
- Gulimette, R.A.**
Inhalation Toxicology Research Institute, Albuquerque, NM
Effective Dose from Inhaled Nuclear Energy Materials, 23
- Gundersen, L.C.S.**
U.S. Geological Survey, Reston, VA
An Investigation of the Geology and Geochemistry of Radon in Sheared and Fractured Rocks, 686
- Gunat, R.**
Southern Methodist University, Dallas, TX
Statistical Examination of Climatological Data Relevant to Global Temperature Variations, 817

Gurley, L.R.

Los Alamos National Laboratory, Los Alamos, NM
Molecular Biology of Cell Cycle Dependent
Genomic Structure, 136
Regulate Mammalian Cell Cycle Progression, 48

Gusfield, D.

Lawrence Berkeley Laboratory, Berkeley, CA
Human Genome Center/Algorithms for Mapping
and Sequencing the Human Genome, 281
University of California, Berkeley, Berkeley, CA
Efficient Algorithms and Data Structures in Support
of DNA Mapping and Sequence Analysis, 343

Gutowski, W.J.

Iowa State University, Ames, IA
Modeling of Land-Surface/Atmospheric Dynamics
for CHAMMP, 751

Haas, M.

University of California, San Diego, La Jolla, CA
Comparative Studies in Mouse and Man, 84

Haber, J.E.

Brandeis University, Waltham, MA
Mechanisms of Repair of Double-Strand
Chromosomal Breaks, 79

Hack, J.J.

National Center for Atmospheric Research,
Boulder, CO
Improvement in Moist and Radiative Processes in
Highly Parallel Atmospheric General
Circulation Models: Validation and
Development Through the CHAMMP
Program, 760

Hahn, F.F.

Inhalation Toxicology Research Institute,
Albuquerque, NM
Links Between Radiation-Induced Lung Cancer
in Laboratory Animals and Humans, 24

Hahn, P.

State University of New York at Syracuse,
Syracuse, NY
Construction of a Human Genome Library
Composed of Multimegabase Acentric
Chromosome Fragments, 385

Hainfeld, J.F.

Brookhaven National Laboratory, Upton, NY
High Resolution DNA Mapping by Scanning
Transmission Electron Microscopy, 261
Radioactive Gold Clusters Bound to Tumor
Antibodies for Cancer Therapy, 446

Hall, C.A.S.

State University of New York at Syracuse,
Syracuse, NY
Spatial and Temporal Patterns of Biotic Exchanges
of CO₂ Between the Atmosphere and Tropical
Landscapes and Their Role in the Global
Carbon Balance, 851

Hall, E.J.

Columbia University, New York, NY
Radiation Physics and Biology, 196

Hameed, W.

State University of New York at Stony Brook,
Stony Brook, NY
Carbon Dioxide-Induced Climate Change, 772

Hamm, R.N.

Oak Ridge National Laboratory, Oak Ridge, TN
Microdosimetry, Biological Modeling, and
Theoretical Biophysics, 188
Pulse-Characterization Neutron Dosimetry, 228

Hankinson, O.

University of California, Laboratory of Biomedical
and Environmental Sciences, Los Angeles, CA
Chemical Carcinogenesis, 83

Hansen, D.K.

Argonne National Laboratory, Argonne, IL
Structural Studies of Site-Specific Mutants of
the Photosynthetic Reaction Center, 108

Hanson, H.P.

University of Colorado, Boulder, CO
Thermohaline Circulations and Global Climate
Change, 799

Harbottle, G.

Brookhaven National Laboratory, Upton, NY
Fundamental Studies of Radon Release from
Soil, 618

Harkema, J.R.

Inhalation Toxicology Research Institute,
Albuquerque, NM
Morphology of the Respiratory Tract and
Response to Injury, 25

Harley, N.H.

New York University Medical Center, New York, NY
Measurement and Apportionment of Radon
Source Terms for Modeling Indoor
Environments, 97

Harling, O.K.

Tufts-New England Medical Center, Boston, MA
A Clinical Trial of Neutron Capture Therapy for
Brain Tumors, 532

Harpel, M.R.

Oak Ridge National Laboratory, Oak Ridge, TN
Protein Chemistry, 145

Hartman, F.C.

Oak Ridge National Laboratory, Oak Ridge, TN
Protein Chemistry, 145
Protein Engineering and Molecular Mutagenesis, 146

Hartman, J.R.

Computational Biosciences, Inc., Ann Arbor, MI
High Performance DNA and Protein Sequence
Analysis on a Low Cost Parallel Processor
Array, 360

Low Cost Massively Parallel Neurocomputing for Pattern Recognition in Macromolecular Sequences, 361

Hayes, K.F.

University of Michigan, Ann Arbor, MI
The Influence of Interfacial Properties on Two-Phase Liquid Flow of Organic Contaminants in Groundwater, 668

Hays, E.F.

University of California, Laboratory of Biomedical and Environmental Sciences, Los Angeles, CA
Hematopoietic Toxicology, 160

Hearst, J.

Lawrence Berkeley Laboratory, Berkeley, CA
Self-Processing Ribonucleic Acid, 425

Hecht, N.B.

Massachusetts Institute of Technology, Cambridge, MA
Robust Detailed Mapping of the Human Genome, 377

Heineman, W.R.

University of Cincinnati, Cincinnati, OH
Development of More Efficacious Tc-99m Organ Imaging Agents, 502

Helt, M.

Environmental Measurements Laboratory, New York, NY
Fallout Radionuclides in Deposition, Diet, and Bone, 212
Pollutants in Deposition and the Biosphere, 546
Pollutants in Surface and Tropospheric Air, 213

Henderson, M.

Cold Spring Harbor Laboratory, Cold Spring Harbor, NY
Human Genetics and Genome Analysis: A Practical Workshop for Public Policymakers and Opinion Leaders, 351

Henderson, R.F.

Inhalation Toxicology Research Institute, Albuquerque, NM
Cellular and Biochemical Mediators of Respiratory Tract Diseases, 26

Hendrey, G.

Brookhaven National Laboratory, Upton, NY
Free Air Carbon Dioxide Field Enrichment Facility Development, 823

Herbes, S.E.

Oak Ridge National Laboratory, Oak Ridge, TN
Mixed-Waste Biodegradation, 637

Herman, J.S.

University of Virginia, Charlottesville, VA
Factors Affecting Transport of Bacterial Cells in Porous Media, 689

The Kinetics of Aromatic-Hydrocarbon Biodegradation and Concomitant Geochemical Reactions Pertinent to Groundwater Systems, 688

Herschman, H.R.

University of California, Laboratory of Biomedical and Environmental Sciences, Los Angeles, CA
Cell Biology and Gene Expression, 161

Hettlich, R.L.

Oak Ridge National Laboratory, Oak Ridge, TN
Isomers and Interactables: Identification of Bio-Adducts, 223

Heymsfield, A.J.

National Center for Atmospheric Research, Boulder, CO
Development and Testing of Parameterizations for Continental and Tropical Ice Cloud Microphysical and Radiative Properties in General Circulation and Mesoscale Models, 812

Hildebrand, C.E.

Los Alamos National Laboratory, Los Alamos, NM
Construction of a Cosmid, Yeast Artificial Chromosome, and Sequence-Tagged Site Physical Map of Human Chromosome 16, 299
Construction of Restriction Maps Using Simulated and Real Data, 310

Himawan, J.

Harvard Medical School, Boston, MA
Thioredoxin-Gene 5 Protein Interactions: Processivity of Bacteriophage T7 DNA Polymerase, 367

Hites, R.A.

Indiana University, Bloomington, IN
Toxic Organic Compounds from Energy Production, 241

Hodgson, K.O.

Stanford Linear Accelerator Center, Stanford, CA
Structural Molecular Biology Support Initiative, 438

Hoffert, M.I.

New York University, New York, NY
Climate Evolution with a Coupled Two-Dimensional Atmospheric/Ocean Model, 766
Cloud and Ocean Effects on Greenhouse Warming, 814

Hoffman, E.J.

University of California, Laboratory of Biomedical and Environmental Sciences, Los Angeles, CA
Nuclear Medicine Applications: Physical Sciences, 493

Hoffman, F.O.

Oak Ridge National Laboratory, Oak Ridge, TN
Radionuclides in the Environment, 630

Holmes, L.

**Oak Ridge Institute of Science and Education,
Oak Ridge, TN**

Human Genome Distinguished Postdoctoral
Fellowships, 313

Postdoctoral Research Program for Global
Change, 824

Holtzman, N.

Columbia University Law School, New York, NY

Lawful Uses of Knowledge from the Human
Genome Project, 358

Hood, L.E.

California Institute of Technology, Pasadena, CA

Biological Information Signal Processor: Very Large
Scale Integration Solutions to Sequence Comparison
Problems, 349

University of Washington, Seattle, WA

Megabase Sequencing of Human Immune
Receptor Loci, 400

Hopke, P.K.

Clarkson University, Potsdam, NY

Radon: Atmospheric Chemistry of Radon Progeny
in Laboratory and Real Indoor Atmospheres, 237

Hopkins, J.A.

**University of Colorado Health Sciences Center,
Denver, CO**

cDNA Sequence-Tagged Site Map of the Human
Genome: Methods Development and
Applications Using Brain cDNAs, 355

Hornberger, G.M.

University of Virginia, Charlottesville, VA

Factors Affecting Transport of Bacterial Cells in
Porous Media, 689

Hosker, Jr., R.P.

**National Oceanic and Atmospheric Administration,
Oak Ridge, TN**

Atmospheric Turbulence and Diffusion Research, 566
Complex Topography in Atmospheric Studies in
Complex Terrain, 567

Hough, P.V.C.

Brookhaven National Laboratory, Upton, NY

Transcription in Eukaryotes, 412

Houghton, R.A.

Woods Hole Research Center, Woods Hole, MA

Spatial and Temporal Patterns of Biotic Exchange
of CO₂ Between the Atmosphere and Tropical
Landscapes and Their Role in the Global
Carbon Balance, 853

Hozier, J.

**State University of New York at Syracuse,
Syracuse, NY**

Construction of a Human Genome Library
Composed of Multimegabase Acentric
Chromosome Fragments, 385

Huang, H.S.-C.

**University of California, Laboratory of Biomedical
and Environmental Sciences, Los Angeles, CA**

Nuclear Medicine Applications:
Biomathematics, 494

Huberman, E.

Argonne National Laboratory, Argonne, IL

Chemical Carcinogenesis Studies in Human and
Rodent Cells, 6

Oncogenes and Human Radiation
Carcinogenesis, 7

Hudson, J.G.

Desert Research Institute, Reno, NV

Linkage of Anthropogenic Aerosol to Clouds
and Climate, 804

Huesman, R.H.

Lawrence Berkeley Laboratory, Berkeley, CA

Human Brain and Heart Metabolism and Flow
Measurements by Noninvasive Techniques, 465

Hughey, B.J.

Science Research Laboratory, Somerville, MA

A New High Yield Cryogenic Target for
Fluorine-18 Production, 523

Hulstrom, R.L.

**National Renewable Energy Laboratory,
Golden, CO**

Atmospheric Radiation Measurements
Program Support, 787

Hunkapiller, T.

California Institute of Technology, Pasadena, CA

Biological Information Signal Processor: Very
Large Scale Integration Solutions to Sequence
Comparison Problems, 349

Lawrence Berkeley Laboratory, Berkeley, CA
Laboratory Information Management System for
Megabase Sequencing, 279

Hurst, G.B.

Oak Ridge National Laboratory, Oak Ridge, TN

Isomers and Interactables: Identification of
Bio-Adducts, 223

Huston, M.A.

Oak Ridge National Laboratory, Oak Ridge, TN

Walker Branch Watershed Project, 700

Hutchinson, J.M.R.

**National Institute of Standards and Technology,
Gaithersburg, MD**

Atom Counting Standards and Doppler Free
RIMS, 246

Illangasekare, T.H.

University of Colorado, Boulder, CO

Studies of Water Infiltration and Runoff in
Subfreezing Snow on Regional Scales to
Estimate Future Greenhouse-Induced
Changes in Sea Level, 743

Imara, M.

Morehouse School of Medicine, Atlanta, GA
Impact of Technology Derived from the Human Genome Project on Genetic Testing, Screening, and Counseling: Cultural, Ethical, and Legal Issues, 380

Inokuti, M.

Argonne National Laboratory, Argonne, IL
Molecular Radiation Physics, 179

Jackson, C.L.

Rhode Island Hospital and Brown University, Providence, RI
An Improved Method for Producing Radiation Hybrids Applied to Human Chromosomes, 391

Jackson, P.J.

Los Alamos National Laboratory, Los Alamos, NM
Plant Physiology, 697

Jacobs, G.K.

Oak Ridge National Laboratory, Oak Ridge, TN
Soil-Water-Contaminant Interactions, 631

Jacobson, K.B.

Oak Ridge National Laboratory, Oak Ridge, TN
Detection of Luminescence from Lanthanide Ions as Labels for DNA Sequencing, 314
DNA Sequence Analysis by Solid-Phase Hybridization, 316
DNA Sequencing Using Stable Isotopes, 317
Using Scanning Tunneling Microscopy to Sequence the Human Genome, 315
Vacuum Ultraviolet Ionizer Mass Spectrometer for Genome Sequencing, 321

Jacobson, R.J.

University of Nevada, Las Vegas, NV
Spatial Variability of Deep Subsurface Micro-Organisms and Correlation with Hydrogeologic Parameters, 670

Jacques, S.L.

University of Texas, M.D. Anderson Cancer Center, Houston, TX
Diagnostic and Therapeutic Applications of Diode Lasers and Solid-State Lasers in Medicine, 529

Jahnke, R.A.

Skidaway Institute of Oceanography, Savannah, GA
Burial, Remineralization, and Utilization of Organic Matter at the Seafloor Under a Strong Western Boundary Current, 602

Jaklevic, J.M.

Lawrence Berkeley Laboratory, Berkeley, CA
Advanced Detectors for Mass Spectroscopy, 277
Human Genome Center/Atomic Force Microscopy/Scanning Tunneling Microscopy, 274
Human Genome Center/Automation and Robotics in Support of the Human Genome Center, 275

Human Genome Center/Fluorescent Detection of Biological Probes, 276

Semiconductor Radiation Detector Technology, 220

Semiconductor X-Ray Detectors for Synchrotrons, 221

James, A.C.

Pacific Northwest Laboratory, Richland, WA
Aerosol Technology Development, 71
Microdosimetry of Radon Daughters, 72

Jardine, P.M.

Oak Ridge National Laboratory, Oak Ridge, TN
Characterization and Microbial Utilization of Organic Carbon, 635
Colloidal Mobility Experiments Using Natural Organics, 634
Field-Scale Validation of Multispecies Transport, 633
Soil-Water-Contaminant Interactions, 631
Subsurface Transport Model Validation and Uncertainty Analysis in Heterogeneous Field Soils, 632

Jastrow, J.D.

Argonne National Laboratory, Argonne, IL
Cooperative Support for the Fermilab National Environmental Research Park, 691

Jaszczak, R.J.

Duke University Medical Center, Durham, NC
Single-Photon Emission Computed Tomography Assay of Radiolabeled Monoclonal Antibodies, 504

Jelenc, P.

Columbia University, New York, NY
Chromosome Specific cDNAs and Sequence-Tagged Sites, 357

Jensen, T.

Colorado State University, Fort Collins, CO
Parameterizations in High Resolution Isopycnal Wind-Driven Ocean Models, 744

Jett, J.H.

Los Alamos National Laboratory, Los Alamos, NM
Rapid DNA Sequencing Based on Fluorescence Detection of Single Molecules, 302

Joel, D.D.

Brookhaven National Laboratory, Upton, NY
Evaluation of Boron Compounds for Neutron Capture Therapy, 451

Johnson, D.R.

University of Wisconsin, Madison, WI
Modeling of Hydrologic and Transport Processes in Relation to Climate Change, 775

Johnson, K.

Brookhaven National Laboratory, Upton, NY
Inorganic Carbon Measurements for the World Ocean Circulation Experiment—Hydrographic Program, 855

- Johnson, N.R.**
Inhalation Toxicology Research Institute,
Albuquerque, NM
Radiation Dose and Injury to Critical Lung Cells
from Radon, 27
- Jones, I.M.**
Lawrence Livermore National Laboratory,
Livermore, CA
Mechanisms of Somatic Mutation in
Mammalian Cells, 44
- Jones, P.D.**
University of East Anglia, Norwich NR47TJ United
Kingdom
Detection of CO₂-Induced Climate Change, 749
- Jones, R.K.**
Inhalation Toxicology Research Institute,
Albuquerque, NM
Protection of Human Subjects, 28
- Joshi, V.**
The Catholic University of America,
Washington, DC
A Bacteriophage T4 In Vitro DNA Packaging
System to Clone Long DNA Molecules, 350
- Jurka, J.**
Linus Pauling Institute of Science and Medicine,
Palo Alto, CA
Efficient Identification and Analysis of Low and
Medium Frequency Repeats, 376
- Kabalka, G.W.**
University of Tennessee Medical Center,
Knoxville, TN
Boron in Nuclear Medicine: New Synthetic
Approaches to Positron Emission Tomography
and Single-Photon Emission Tomography
Agents, 528
- Kahl, S.B.**
University of California, San Francisco School of
Pharmacy, San Francisco, CA
Carboranyl Amino Acids for Site-Specific
Neutron Capture Therapy of Malignant
Melanoma, 498
- Kanciruk, P.**
Oak Ridge National Laboratory, Oak Ridge, TN
Database Support to Assist in Quantifying the
Link Between Changes in Atmospheric
Composition and Climate Change, 788
- Kane, D.L.**
University of Alaska, Fairbanks, AK
Arctic Hydrology and Meteorology, 708
- Kao, C.Y.J.**
Los Alamos National Laboratory, Los Alamos, NM
Cloud Parameterization in Climate Models, 786
- Interfacing Between a Hierarchy of Numerical
Models in the Atmospheric Radiation
Measurement Program, 785
- Kao, F.-T.**
University of Colorado Health Sciences Center,
Denver, CO
Chromosome Region-Specific Libraries for
Human Genome Analysis, 356
- Kapp, O.H.**
University of Chicago, Chicago, IL
Electron Microscope Development, 441
- Karam, L.R.**
National Institute of Standards and Technology,
Gaithersburg, MD
Radon: Energy Deposition and Radiation Quality of
Radon and Radon Daughters, 244
- Karger, B.L.**
Northeastern University, Boston, MA
The Separation of DNA by Pulsed Field Capillary
Electrophoresis, 387
- Karin, M.**
University of California, San Diego, La Jolla, CA
The Molecular Basis for Ultraviolet Response of
Cultured Human Cells, 164
- Karl, T.**
Columbia University, Palisades, NY
Recent Changes of Weather Patterns in
North America, 748
- Karl, T.R.**
National Climatic Data Center, Asheville, NC
Climatological Aerological (Upper Air) Reference
Data Set, 763
Data Preparation and Analysis for Annex III, U.S./
People's Republic of China Cooperation in the
Field of Atmospheric Trace Gases, 762
- Karp, J.**
University of Pennsylvania, Philadelphia, PA
Positron Ring System Using Angle-Type
Detectors, 521
- Kasha, M.**
Florida State University, Tallahassee, FL
Energy Transformation in Molecular Electronic
Systems, 197
- Katsouros, M.H.M.**
National Academy of Sciences, Washington, DC
Ocean Studies Board, 861
Support of the Ocean Studies Board, 591
- Katz, J.**
Lawrence Berkeley Laboratory, Berkeley, CA
Advanced Detectors for Mass Spectroscopy, 277
- Katz, R.**
University of Nebraska, Lincoln, NE
Theory of Relative Biological Effectiveness, 203

Katzellenbogen, J.A.

University of Illinois, Urbana, IL
Fluorine-18-Labeled Androgens and Progestins:
Imaging Agents for Tumors of Prostate and
Breast, 507

Keeling, C.D.

Scripps Institution of Oceanography, La Jolla, CA
A Study of the Abundance and $^{13}\text{C}/^{12}\text{C}$ Ratio of
Atmospheric Carbon Dioxide and Oceanic
Carbon in Relation to the Global Carbon
Cycle, 848

Oceanic CO_2 Measurements for the World Ocean
Circulation Experiment Hydrographic Survey
in the Pacific Ocean, 1990-1991: Shore-Based
Analysis During LEG 1-3, 863

Oceanic CO_2 Measurements for the World Ocean
Circulation Experiment Hydrographic Survey
of the Pacific Ocean: Shipboard Alkalinity
Analyses During 1991 and 1992, 864

Kegelmeyer, Jr., P.W.

Sandia National Laboratories, Livermore, CA
Passive Cloud Dynamics Measurement—A Flow
Field Registration Approach, 797

Keller, R.

University of Arizona, Tucson, AZ
Single-Molecule Detection Using Charge Coupled
Device Array Technology, 331

Keller, R.A.

Los Alamos National Laboratory, Los Alamos, NM
Rapid DNA Sequencing Based on Fluorescence
Detection of Single Molecules, 302

Kelley, J.

The Institute for Genomic Research,
Gaithersburg, MD
Expressed Sequence Tags from Human Brain
cDNAs for Genome Mapping, 370

Kelly, G.

Inhalation Toxicology Research Institute,
Albuquerque, NM
Molecular Mechanisms of Radiation-Induced
Cancer, 29

Kemp, P.

Brookhaven National Laboratory, Upton, NY
Measurement of Marine Microbial Growth, 577
Microbial Processes in Coastal Marine
Systems, 576

Kennedy, R.A.

Pacific Northwest Laboratory, Richland, WA
Chernobyl Database, 232

Kennel, S.J.

Oak Ridge National Laboratory, Oak Ridge, TN
Monoclonal Antibodies for Study of
Metastases, 477

Kerlavage, A.

The Institute for Genomic Research,
Gaithersburg, MD
Expressed Sequence Tags from Human Brain
cDNAs for Genome Mapping, 370

Kerr, G.D.

Oak Ridge National Laboratory, Oak Ridge, TN
Medical Physics and Internal Dosimetry, 224

Khall, M.A.K.

Oregon Graduate Institute of Science
and Technology, Beaverton, OR
Methane Fluxes from Rice Fields in China: Spatial
and Temporal Variability and Estimates of
Contributions to the Global Budget, 767

Khan, A.S.

University of Colorado Health Sciences Center,
Denver, CO
cDNA Sequence-Tagged Site Map of the Human
Genome: Methods Development and Applications
Using Brain cDNAs, 355

Kloft, T.L.

New Mexico Institute of Mining and Technology,
Socorro, NM

Water Potential in Relation to Numbers and
Activities of Microbes in Saturated and
Unsaturated Subsurface Environments, 671

Klehl, J.T.

National Center for Atmospheric Research,
Boulder, CO
A Hierarchical Approach to Improved Cloud-
Radiation Parameterizations for Climate
Models Through the Atmospheric Radiation
Measurement Program, 811

Kim, S-H.

Lawrence Berkeley Laboratory, Berkeley, CA
Catalytic Antibodies, 429
Multiuser Crystallography Facility, 427
Structural Biophysics, 426

Kimball, B.

U.S. Department of Agriculture-Agricultural Research
Service, Phoenix, AZ
Elevated CO_2 : Modeling Cotton Response
Interactions with Temperature on Photosynthesis,
Insect Population Dynamics and Temperature
Interactions and Long-term Effects on Trees, 833

Kinter, J.L.

University of Maryland, College Park, MD
Variability and Predictability of the Coupled
Ocean-Atmosphere-Land Climate System, 753

Kirz, J.

State University of New York at Stony Brook,
Stony Brook, NY
X-Ray Micro-imaging by Diffractive
Techniques, 444

Klein, M.

Lawrence Berkeley Laboratory, Berkeley, CA
Biophysical Chemistry, 428

Kleinman, L.I.

Brookhaven National Laboratory, Upton, NY
Continental and Oceanic Fate of Energy-Related
Air Pollutants, 541

Radiative Properties of Nonuniform Clouds, 778

Klots, C.E.

Oak Ridge National Laboratory, Oak Ridge, TN
Chemical Physics Studies in the Gaseous and
Liquid Phases, 186

Ion Chemistry and Molecular Clustering
Phenomena, 189

Knapp, E.A.

Santa Fe Institute, Santa Fe, NM
A Broad Research Program on the Sciences of
Complexity, 769

Knapp, R.B.

Lawrence Livermore National Laboratory,
Livermore, CA

Application of Particle Methods to
Multicomponent Geochemical Reactive
Transport Problems, 628

Knapp, Jr., F.F.

Oak Ridge National Laboratory, Oak Ridge, TN
Biomedical Radioisotope Technology
Development, 479

Nuclear Medicine and Biomedical Radioisotope
Technology, 478

Kocher, D.C.

Oak Ridge National Laboratory, Oak Ridge, TN
Medical Physics and Internal Dosimetry, 224

Koetzle, T.F.

Brookhaven National Laboratory, Upton, NY
Protein Data Bank Operations, 264

Kopelman, R.

University of Michigan, Ann Arbor, MI
Nanometer Scale Exciton Spectroscopy and
Photochemistry: Dynamic Imaging of DNA
Structure-Activity Relations and Radiation
Signatures, 242

Scanning Molecular Exciton Microscopy: A New
Approach to Gene Sequencing, 378

Korenberg, J.R.

University of California, Cedars—Sinai Medical
Center, Los Angeles, CA

Human cDNA Mapping Using Fluorescence In Situ
Hybridization, 345

Kouprina, N.

National Institute of Environmental Health Science,
Research Triangle Park, NC

Genetic Analysis of Yeast Artificial
Chromosome Following Yeast
Transformation and Mitotic Growth, 303

Kraemer, P.M.

Los Alamos National Laboratory, Los Alamos, NM
Karyotype Instability and Neoplasia Studies, 137

Kristofferson, D.

Intelligenetics Inc, Mountain View, CA
The BIOSCI Electronic Newsgroup Network for the
Biological Sciences, 371

Kropfli, R.A.

National Center for Atmospheric Research,
Boulder, CO

Shipboard Measurements of the Cloud-Capped
Marine Boundary Layer During Fire/Atlantic
Stratocumulus Transition Experiment, 813

Kryter, R.C.

Oak Ridge National Laboratory, Oak Ridge, TN
Widely Deployable Low Cost Radiometer for the
Atmospheric Radiation Measurement Program
Extended Observing Stations, 789

Kuhl, D.E.

University of Michigan Medical Center,
Ann Arbor, MI

New Techniques for Positron Emission
Tomography in the Study of Human
Neurological Disorders, 513

Radiopharmaceuticals for Diagnosis and
Treatment, 514

Kukla, G.

Columbia University, Palisades, NY
Recent Changes of Weather Patterns in
North America, 748

Kulp, T.J.

Lawrence Berkeley Laboratory, Berkeley, CA
An Investigation of Chemical Flow Characteristics
Using Fiber Optic Sensor Technology, 627

Lawrence Livermore National Laboratory,
Livermore, CA

Spectroscopic Study of H₂O Absorption in the
8- to 14-Micrometer Atmospheric Window:
Measurement of New Line and Continuum
Parameters and Investigation of Far-Wing
Phenomena, 781

Kumar, D.

Louisiana State University, Baton Rouge, LA
A Physicochemical Study of Some Areas of
Fundamental Significance to Biophysics, 199

LLaoer, J.

Lawrence Berkeley Laboratory, Berkeley, CA
Application of Statistically Based Algorithms to
Emission Tomography, 463

Lacks, S.A.

Brookhaven National Laboratory, Upton, NY
Reactions of DNA Within Cells, 112

Lambropoulos, P.

University of Southern California, Los Angeles, CA
Theoretical Problems in Laser Spectroscopy of
Atoms and Molecules, 253

Lane, M.J.

State University of New York at Syracuse,
Syracuse, NY
Construction of a Human Genome Library
Composed of Multimegabase Acentric
Chromosome Fragments, 385

Langlois, R.G.

Lawrence Livermore National Laboratory,
Livermore, CA
Human Mutagenesis: Methods, Applications,
Animal Models, and Mechanisms, 128

Langmore, J.

University of Michigan, Ann Arbor, MI
Scanning Molecular Exciton Microscopy: A
New Approach to Gene Sequencing, 378

Lapp, M.

Sandia National Laboratory, Livermore, CA
Laser Remote Sensing of Water Vapor, 796

Larimer, F.W.

Oak Ridge National Laboratory, Oak Ridge, TN
Detection of Luminescence from Lanthanide Ions
as Labels for DNA Sequencing, 314
DNA Sequencing Using Stable Isotopes, 317
Protein Engineering and Molecular Mutagenesis, 146

Larionov, V.

National Institute of Environmental Health Science,
Research Triangle Park, NC
Genetic Analysis of Yeast Artificial Chromosome
Following Yeast Transformation and Mitotic
Growth, 303

Larsen, I.L.

Oak Ridge National Laboratory, Oak Ridge, TN
Radionuclides in the Coastal Zone, 702

Larson, S.M.

Sloan-Kettering Institute for Cancer Research,
New York, NY
Biomedical Research with Cyclotron-Produced
Radionuclides, 524

Laulainen, N.S.

Pacific Northwest Laboratory, Richland, WA
Network-Based Solar and Meteorological
Characterization of Cloud-Radiation Effects
in Global Climate Modeling, 792

Lawler, E.

University of California, Berkeley, Berkeley, CA
Efficient Algorithms and Data Structures in
Support of DNA Mapping and Sequence
Analysis, 343
Lawrence Berkeley Laboratory, Berkeley, CA
Human Genome Center/Algorithms for Mapping
and Sequencing the Human Genome, 281

Lawrence, C.

Baylor College of Medicine, Houston, TX
Genome Assembly Manager, 335

Lawrence, C.W.

University of Rochester School of Medicine,
Rochester, NY
Molecular Mechanisms of Misrepair
Mutagenesis, 175

Lawson, C.L.

Brookhaven National Laboratory, Upton, NY
Structural Studies on Proteins by X-Ray
Diffraction, 413

Lechner, J.F.

Inhalation Toxicology Research Institute,
Albuquerque, NM
Lung Cancer in Uranium Miners—Gene
Dysfunctions, 32
Mechanism of Radiation-Induced Cancer, 31
Premalignant Events in Radiation-Induced
Lung Cancer, 30

Lee, J.T.

Los Alamos National Laboratory,
Los Alamos, NM
Terrain-Influenced Meteorology, 551

Lee, S.Y.

Oak Ridge National Laboratory, Oak Ridge, TN
Mixed-Waste Biodegradation, 637

Lee, W.R.

Louisiana State University, Baton Rouge, LA
Mutagenic Effects of Tritium on DNA of *Drosophila*
melanogaster, 169

Lee, Y.N.

Brookhaven National Laboratory, Upton, NY
Atmospheric Organic Chemistry: Investigation of
Primary and Secondary Species, 544
Continental and Oceanic Fate of Energy-Related
Air Pollutants, 541

Leggett, R.W.

Oak Ridge National Laboratory, Oak Ridge, TN
Medical Physics and Internal Dosimetry, 224

Lehnert, B.E.

Los Alamos National Laboratory, Los Alamos, NM
Pulmonary Damage, 138

- Lelehner, P.K.**
The University of Nebraska Medical Center,
Omaha, NE
Dosimetry & Quantitative Radionuclide Imaging
in Radioimmunotherapy, 518
- Leifer, R.**
Environmental Measurements Laboratory,
New York, NY
Atmospheric Radiation Measurement Program
Support, 779
- Lemanski, C.L.**
Los Alamos National Laboratory, Los Alamos, NM
Sequencing and Mapping of cDNAs from a
Paternal Encoded Human Pregnancy, 300
- Lempiok, A.**
ALEM Associates, Boston, MA
Improved Scintillator Materials for Medical
Applications, 482
Boston University, Boston, MA
Scintillation Materials for Medical
Applications, 487
- Lennon, G.**
Lawrence Livermore National Laboratory,
Livermore, CA
Coding Region Isolation, Mapping, and
Characterization, 290
Interdigitation of the Physical and Generic Maps
of Human Chromosome 19, 291
- Leon, E.**
Intelligenetics Inc, Mountain View, CA
The BIOSCI Electronic Newsgroup Network for
the Biological Sciences, 371
- Leone, Jr., J.M.**
Lawrence Livermore National Laboratory,
Livermore, CA
Mesoscale Emergency Response, 549
- Lerman, L.S.**
Massachusetts Institute of Technology,
Cambridge, MA
Robust Detailed Mapping of the Human Genome, 377
- Lesko, S.A.**
The Johns Hopkins University School of Hygiene and
Public Health, Baltimore, MD
Genes and Gene Expression: Localization, Damage,
and Control—A Multilevel and Interdisciplinary
Study, 168
- Levy, A.**
Brookhaven National Laboratory, Upton, NY
A Regional Cyclotron-Positron Emission
Tomography Center for Radiotracer Research
and Medical Application, 447
- Lewis, S.**
Lawrence Berkeley Laboratory, Berkeley, CA
Laboratory Information Management System for
Megabase Sequencing, 279
- Liang, L.**
Oak Ridge National Laboratory, Oak Ridge, TN
Colloidal Mobility Experiments Using Natural
Organics, 634
- Liburdy, R.P.**
Lawrence Berkeley Laboratory, Berkeley, CA
Biological Effects of Magnetic Fields, 40
- Lim, H.A.**
Florida State University, Tallahassee, FL
Multiple Alignment and Homolog Sequence
Database Compilation, 366
- Lincoln, D.E.**
University of South Carolina, Columbia, SC
Herbivore Responses to Plants Grown in
Enriched CO₂ Atmosphere, 850
- Lindberg, S.E.**
Oak Ridge National Laboratory, Oak Ridge, TN
Atmosphere-Canopy Interactions, 552
- Ling, C.C.**
Sloan Kettering Memorial Cancer Center,
New York, NY
Activation of Oncogenes by Radon Progeny
and X Rays, 99
- Linn, S.**
University of California, Berkeley, Berkeley, CA
Endonucleases Involved in Repair and
Recombination of DNA, 155
- Lobb, R.**
Los Alamos National Laboratory,
Los Alamos, NM
Sequencing and Mapping of cDNAs from a
Paternal Encoded Human Pregnancy, 300
- Lohrenz, S.E.**
University of Southern Mississippi,
Stennis Space Center, MS
Development of a Multisensor In Situ Fiber
Optic Fluorometer, 604
- Long, J.C.S.**
Lawrence Berkeley Laboratory, Berkeley, CA
An Interdisciplinary Approach to Spatial
Characterization of Contaminant Transport, 624
- Long, P.E.**
Pacific Northwest Laboratory, Richland, WA
Deep Microbiology Geosciences Testing, 649
Microbial Origin/Transport in Subsurface
Systems, 651
- Longmire, J.L.**
Los Alamos National Laboratory,
Los Alamos, NM
Human Recombinant DNA Library, 298

Loe, J.A.

Pacific Northwest Laboratory, Richland, WA
Ion Cyclotron Resonance Mass Spectroscopy
of DNA Molecular Ions, 324

Lowder, W.

Environmental Measurements Laboratory,
New York, NY
Environmental Radiation Research, 215
Radiation Transport and Dosimetry, 214
Radon, Thoron, and the Related Aerosols, 216

Lowery, R.

Promega Corporation, Madison, WI
Site-Specific Endonucleases for Human
Genome Mapping, 389

Lu, P.Y.

Oak Ridge National Laboratory, Oak Ridge, TN
Radon Information Transfer, 64

Lucas, J.N.

Lawrence Livermore National Laboratory,
Livermore, CA
Flow and Analytical Cytogenetics, 131

Lucatorto, T.B.

National Institute of Standards and Technology,
Gaithersburg, MD
Atom Counting Standards and Doppler Free
RIMS, 246

MacCracken, M.C.

Lawrence Livermore National Laboratory,
Livermore, CA
Carbon Dioxide Effects Research, 725
Computer Hardware Advanced, Mathematics,
and Model Physics Initiative Organization, 726

MacDonnell, M.T.

Ransom Hill Bioscience, Ramona, CA
High Speed Electrophoresis in a Solid Substrate, 390

MacInnes, M.A.

Los Alamos National Laboratory, Los Alamos, NM
Transgenic Cell Models of Human Radiation
Sensitivity, 49

Macken, C.

Los Alamos National Laboratory,
Los Alamos, NM
Pooling Yeast Artificial Chromosome Libraries
for Screening with Unique Sequences, 296

Maglott, D.R.

American Type Culture Collection, Rockville, MD
Multiplex Mapping of Human cDNAs, 330

Mahaffey, J.A.

Pacific Northwest Laboratory, Richland, WA
Chernobyl Database, 232

Major, E.L.

Lawrence Berkeley Laboratory, Berkeley, CA
An Interdisciplinary Approach to
Spatial Characterization of Contaminant
Transport, 624

Makarov, V.

University of Michigan, Ann Arbor, MI
Scanning Molecular Exciton Microscopy: A New
Approach to Gene Sequencing, 378

Malone, R.C.

Los Alamos National Laboratory, Los Alamos, NM
Computer Hardware, Advanced Mathematics, and
Model Physics, 729

Mangel, W.F.

Brookhaven National Laboratory, Upton, NY
The Roles of Proteases in Normal and Abnormal
Physiological Processes, 113

Mansfield, B.K.

Oak Ridge National Laboratory, Oak Ridge, TN
Human Genome Management Information
System, 322

Margolin, L.G.

Los Alamos National Laboratory, Los Alamos, NM
Predictability in Numerical Modeling of Ocean
Dynamics, 731

Marinelli, W.J.

Physical Sciences, Inc., Andover, MA
An Imaging Fabry-Perot Spectrometer for Site
Evaluation of Trace Species, 680
An Imaging Fabry-Perot Spectrometer for Site
Evaluation of Trace Species, 250

Mark, H.F.L.

Rhode Island Hospital and Brown University,
Providence, RI
An Improved Method for Producing Radiation
Hybrids Applied to Human Chromosomes, 391

Markham, O.D.

Idaho National Engineering Laboratory,
Idaho Falls, ID
INEL National Environmental Research
Park, 695
INEL Radioecology and Ecology Program, 622

Markowitz, V.M.

Lawrence Berkeley Laboratory, Berkeley, CA
Human Genome Center/Database Tools for
Scientific Applications, 278
Laboratory Information Management System for
Megabase Sequencing, 279

Marley, N.A.

Argonne National Laboratory, Argonne, IL
Atmospheric Chemistry of Organic Oxidants
and Aldehydes, 537
Investigation of Organic/Inorganic Complexation
Processes in Subsurface Environments, 615

- Mechanisms of Colloidal Transport in Groundwater Environments**, 614
- Marlow, W.H.**
Texas A&M University, College Station, TX
Atmospheric Aerosol Microphysics Formation, Characterization, and Interaction, 572
- Marr, T.G.**
Cold Spring Harbor Laboratory,
Cold Spring Harbor, NY
A Computer System for Access to Distributed Genome Mapping Data, 352
- Marrone, B.L.**
Los Alamos National Laboratory, Los Alamos, NM
High Precision Mapping of Yeast Artificial Chromosome Clones onto Chromosome 21 by Fluorescence In Situ Hybridization and Image Analysis, 304
- Martin, C.**
Lawrence Berkeley Laboratory, Berkeley, CA
Human Genome Center/100 Megabase Physical Mapping, 272
Human Genome Center/Large Scale DNA Sequencing, 271
- Martin, C.B.**
Tropix, Inc., Bedford, MA
Chemiluminescent Multiprimed DNA Sequencing, 397
- Martin, J.C.**
Los Alamos National Laboratory,
Los Alamos, NM
Rapid DNA Sequencing Based on Fluorescence Detection of Single Molecules, 302
- Martin, S.A.**
Oak Ridge National Laboratory, Oak Ridge, TN
Human Genome Management Information System, 322
- Masden, E.L.**
Cornell University, Ithaca, NY
Comparison of Distribution, Abundance, and Activities of Deep Subsurface Micro-Organisms at DOE Sites, 658
- Matheison, N.W.**
The Johns Hopkins University School of Medicine,
Baltimore, MD
A Human Genome Database, 372
- Mathies, R.A.**
University of California, Berkeley, Berkeley, CA
Ultrasensitive Fluorescence Detection of DNA, 342
- Mausner, L.F.**
Brookhaven National Laboratory, Upton, NY
Radioactive Gold Clusters Bound to Tumor Antibodies for Cancer Therapy, 446
- Mayer, L.M.**
University of Maine, Walpole, ME
Adsorption Control of Organic Carbon Burial in Ocean Margin Sediments, 588
- Mazur, P.**
Oak Ridge National Laboratory, Oak Ridge, TN
Theoretical and Applied Cryobiology, 147
- Mazziotta, J.C.**
University of California, Laboratory of Biomedical and Environmental Sciences,
Los Angeles, CA
Nuclear Medicine Applications:
Neuroscience, 495
- McAllister, D.J.**
BIODE, Inc., Cape Elizabeth, ME
An Acoustic Plate Mode DNA Biosensor, 339
- McCamant, L.**
Oak Ridge Institute for Science and Education,
Oak Ridge, TN
Alexander Hollaender Distinguished Postdoctoral Fellowships, 53
- McCarthy, J.F.**
Oak Ridge National Laboratory, Oak Ridge, TN
Characterization and Microbial Utilization of Organic Carbon, 635
Colloidal Mobility Experiments Using Natural Organics, 634
Mobility of Microorganisms in a Sandy Aquifer, 636
- McCarthy, J.L.**
Lawrence Berkeley Laboratory, Berkeley, CA
Human Genome Center/Information Management System, 280
- McCleary, D.**
Oak Ridge Institute for Science and Education,
Oak Ridge, TN
OHER/Historically Black Colleges and Universities Faculty and Student Research Participation Program, 54
- McCormick, J.J.**
Michigan State University College of Osteopathic Medicine, East Lansing, MI
Malignant Transformation of Diploid Human Fibroblasts by Transfection of Oncogenes, 171
- McCormick, M.K.**
Los Alamos National Laboratory, Los Alamos, NM
Construction and Characterization of Human Genomic Yeast Artificial Chromosome Library with a Low Frequency of Chimeric Clones, 308
Construction of a Cosmid, Yeast Artificial Chromosome, and Sequence-Tagged Site Physical Map of Human Chromosome 16, 299
High Precision Mapping of Yeast Artificial Chromosome Clones onto Chromosome 21 by Fluorescence In Situ Hybridization and Image Analysis, 304

- Human Recombinant DNA Library, 298
- Pooling Yeast Artificial Chromosome Libraries for Screening with Unique Sequences, 296
- McEntee, K.**
University of California, Laboratory of Biomedical and Environmental Sciences, Los Angeles, CA
DNA Damage and Gene Expression, 162
- McGlynn, S.P.**
Louisiana State University, Baton Rouge, LA
A Physicochemical Study of Some Areas of Fundamental Significance to Biophysics, 199
- Molnerney, J.D.**
Colorado College, Colorado Springs, CO
Mapping & Sequencing the Human Genome: Science, Ethics, & Public Policy Development & Distribution of Educational Materials for Use in High School Biology Classes, 354
- McKinley, J.P.**
Pacific Northwest Laboratory, Richland, WA
Pore Water Chemistry, 650
- McKoy, V.**
California Institute of Technology, Pasadena, CA
Resonance Enhanced Multiphoton Ionization Spectra of Molecules and Molecular Spectra, 236
- McKusick, V.A.**
The Johns Hopkins University School of Medicine, Baltimore, MD
A Human Genome Database, 372
- McMurry, P.H.**
University of Minnesota, Minneapolis, MN
Ultrafine Aerosol Size Distributions and Sulfuric Acid Vapor Pressures: Implications for New Particle Formation in the Atmosphere, 565
- McPherson, D.W.**
Oak Ridge National Laboratory, Oak Ridge, TN
Nuclear Medicine and Biomedical Radioisotope Technology, 478
- McPherson, J.D.**
Los Alamos National Laboratory, Los Alamos, NM
Systematic Generation of Chromosome 5 Specific Sequence-Tagged Sites, 301
- Mead, D.**
University of Wisconsin, Madison, WI
Automation of the Front End of DNA Sequencing, 403
- Mease, R.C.**
Brookhaven National Laboratory, Upton, NY
Synthesis of New Rigid Chelating Agents for Preparing Stable Radiometal Immunoconjugates, 452
- Mechoso, C.R.**
University of California, Los Angeles, Los Angeles, CA
Development of an Advanced Finite-Difference Atmospheric General Circulation Model, 741
- Medvick, P.A.**
Los Alamos National Laboratory, Los Alamos, NM
Automated Methods for Large Scale Physical Mapping, 312
- Meehl, G.**
National Center for Atmospheric Research, Boulder, CO
Enhanced Research Program on the Long-Range Climatic Effects of Increasing Atmospheric Carbon Dioxide, 761
- Meier, M.F.**
University of Colorado, Boulder, CO
Studies of Water Infiltration and Runoff in Subfreezing Snow on Regional Scales to Estimate Future Greenhouse-Induced Changes in Sea Level, 743
- Melnhold, C.**
National Council on Radiation Protection and Measurements, Bethesda, MD
Development of Recommendations on Radiation Protection and Measurements, 243
- Melli, S.H.**
Sandia National Laboratory, Livermore, CA
Laser Remote Sensing of Water Vapor, 796
- Mercer, R.R.**
Duke University Medical Center, Durham, NC
Determination of the Cell Distribution and Mucous Thickness in the Airways of the Lung for Modeling Injury Caused by Inhaled Radon and Radon Daughters, 88
- Meyne, J.**
Los Alamos National Laboratory, Los Alamos, NM
Genome Organization and Function, 306
Strand-Specific Orientation of Satellite DNA Sequences Determined by Fluorescence In Situ Hybridization, 305
- Micklos, D.A.**
Cold Spring Harbor Laboratory, Cold Spring Harbor, NY
Human Genetics and Genome Analysis: A Practical Workshop for Public Policymakers and Opinion Leaders, 351
- Miller, A.**
Scripps Institution of Oceanography, La Jolla, CA
Studies of Ocean Predictability at Decade to Century Time Scales Using a Global Ocean General Circulation Model in a Parallel Computing Environment, 770
- Miller, J.C.**
Oak Ridge National Laboratory, Oak Ridge, TN
Chemical Kinetics of Irradiated Materials, 183
Chemical Physics Studies in the Gaseous and Liquid Phases, 186

- Ion Chemistry and Molecular Clustering Phenomena, 189
Nanosecond and Picosecond Nonlinear Laser Techniques, 226
Resonance Ionization Spectroscopy, 225
- Miller, J.H.**
Pacific Northwest Laboratory, Richland, WA
Modeling Cellular Responses to Genetic Damage, 193
- Miller, P.S.**
The Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD
Genes and Gene Expression: Localization, Damage, and Control—A Multilevel and Interdisciplinary Study, 168
- Miller, R.J.**
Pacific Northwest Laboratory, Richland, WA
Lasers in Environmental Research, 233
- Miller, R.M.**
Argonne National Laboratory, Argonne, IL
Stress Tolerance Strategies in Plant/Soil Systems, 692
- Miller, A.L.**
University of Virginia, Charlottesville, VA
Factors Affecting Transport of Bacterial Cells in Porous Media, 689
- Minner, D.**
Oak Ridge Institute for Science and Education, Oak Ridge, TN
Technical Support for Implementation of the DOE Human Subject Policy, 52
- Mirzadeh, S.**
Oak Ridge National Laboratory, Oak Ridge, TN
Biomedical Radioisotope Technology Development, 479
Nuclear Medicine and Biomedical Radioisotope Technology, 478
- Mishra, N.C.**
University of South Carolina, Columbia, SC
Characterization of Mammalian DNA Polymerase Gene(s) and Protein(s), 177
- Misra, R.**
University of North Carolina, Chapel Hill, NC
Development of Human Viral-Based Genomic Library of 150 to 200 Kb Inserts, 386
- Mitra, S.**
Oak Ridge National Laboratory, Oak Ridge, TN
Mutations in Shuttle Plasmids, 62
Protein Engineering and Molecular Mutagenesis, 146
Protein-Nucleic Acid Interactions, 148
- Mohrenwieser, H.W.**
Lawrence Livermore National Laboratory, Livermore, CA
Assembly, Closure, and Characterization of a Chromosome 19 Contig Map, 292
Coding Region Isolation, Mapping, and Characterization, 290
Core Facility, 287
Human Germinal Gene Mutation Project, 129
Interdigitation of the Physical and Genetic Maps of Human Chromosome 19, 291
- Mohr, D.T.**
Collaborative Research, Inc., Waltham, MA
Chimera-Free, High Copy Number Yeast Artificial Chromosome Libraries and Efficient Methods of Analysis, 353
- Moolgavkar, S.H.**
Fred Hutchinson Cancer Research Center, Seattle, WA
Initiation-Promotion-Initiation Experiments with Radon and Cigarette Smoke: Lung Tumors in Rats, 89
- Moore, S.**
WNET/THIRTEEN, New York, NY
Medicine at the Crossroads, 407
- Moore, III, B.**
University of New Hampshire, Durham, NH
Spatial and Temporal Patterns of Biotic Exchanges of CO₂ Between the Atmosphere and Tropical Landscapes and Their Role in the Global Carbon Balance, 845
- Moreno, R.**
The Institute for Genomic Research, Gaithersburg, MD
Expressed Sequence Tags from Human Brain cDNAs for Genome Mapping, 370
- Morgan, W.F.**
University of California, San Francisco, San Francisco, CA
Elucidation of Cytogenetic Damage, 16
- Morris, D.E.**
Los Alamos National Laboratory, Los Alamos, NM
Co-Contaminant Reaction Chemistry at Interfaces, 629
- Morris, M.J.**
Ocean Optics, Inc., Dunedin, FL
Inherently Calibrated Fiber Optic Sensors for Measuring Seawater pH, 596
- Morrison, G.H.**
Cornell University, Ithaca, NY
Subcellular Distribution of Boron for Boron Neutron Capture Therapy Using Ion Microscopy, 503

Mortimer, R.K.

Lawrence Berkeley Laboratory, Berkeley, CA
Genetic Study on Yeast, 124

Moseley, R.E.

Morehouse School of Medicine, Atlanta, GA
Impact of Technology Derived from the
Human Genome Project on Genetic Testing,
Screening, and Counseling: Cultural, Ethical,
and Legal Issues, 380

Moyzis, R.K.

Los Alamos National Laboratory, Los Alamos, NM
Center for Human Genome Studies, 295
Construction and Characterization of Human
Genomic Yeast Artificial Chromosome Library
with a Low Frequency of Chimeric Clones, 308
Construction of a Cosmid, Yeast Artificial
Chromosome, and Sequence-Tagged Site
Physical Map of Human Chromosome 16, 299
Genetic Analysis of Yeast Artificial Chromosome
Following Yeast Transformation and Mitotic
Growth, 303
Genome Organization and Function, 306
Human Recombinant DNA Library, 298
Systematic Generation of Chromosome 5 Specific
Sequence-Tagged Sites, 301

Mucenki, M.L.

Oak Ridge National Laboratory, Oak Ridge, TN
Mapping in Mouse-Human Homologous Regions, 318

Muenter, J.B.

University of Rochester, Rochester, NY
Intermolecular Potential Functions from
Spectroscopic Properties of Weakly Bound
Complexes, 206

Muggenburg, B.A.

Inhalation Toxicology Research Institute,
Albuquerque, NM
Dose-Response Relationships for Inhaled
Radionuclides, 33

Mulholland, P.J.

Oak Ridge National Laboratory, Oak Ridge, TN
Walker Branch Watershed Project, 700

Munk, C.

Los Alamos National Laboratory, Los Alamos, NM
Construction and Characterization of Human Genomic
Yeast Artificial Chromosome Library with a Low
Frequency of Chimeric Clones, 308

Munk, W.

Scripps Institution of Oceanography, La Jolla, CA
Acoustic Global Warming Feasibility Experiment, 865

Mural, R.J.

Oak Ridge National Laboratory, Oak Ridge, TN
Mapping in Mouse-Human Homologous Regions, 318
Protein Engineering and Molecular Mutagenesis, 146

Murray, D.G.

University of Denver, Denver, CO
Development of a Short-Wavelength Infrared Solar
Spectral Radiometer for the Atmospheric Radiation
Measurement Program, 803

Murnane, J.

University of California, San Francisco,
San Francisco, CA
DNA Replication and Repair, 119

Murphy, D.C.

The Library of Congress, Washington, DC
Pilot Resident Fellow Program in Science and
Technology: Bioethics Issues in Molecular
Genetics, 375

Murphy, E.M.

Pacific Northwest Laboratory, Richland, WA
Microbial Origin/Transport in Subsurface Systems, 651

Nagle, J.

The Institute for Genomic Research, Gaithersburg, MD
Expressed Sequence Tags from Human Brain cDNAs
for Genome Mapping, 370

Narasimhan, T.N.

Lawrence Berkeley Laboratory, Berkeley, CA
Experimental and Theoretical Investigations of Radon
Availability, Migration, and Entry, 623

Naris, M.

Lawrence Berkeley Laboratory, Berkeley, CA
Bone Marrow Stem Cells and Stromal
Microenvironment, 41

Natowicz, M.

Eunice Kennedy Shriver Center for
Mental Retardation, Waltham, MA
Studies of Genetic Discrimination, 364

Neel, J.V.

University of Michigan, Ann Arbor, MI
Studies of Human Mutation Rates, 91

Nelson, D.

Lawrence Livermore National Laboratory,
Livermore, CA
Computational Support for the Human Genome
Center: Statistical and Mathematical Analysis,
Data Processing, and Databasing, 286

Nelson, D.L.

Baylor College of Medicine, Houston, TX
Isolation of cDNAs from the Human X Chromosome
and Derivation of Related Sequence-Tagged
Sites, 337

Nelson, J.M.

Pacific Northwest Laboratory, Richland, WA
Radiation Biophysics, 194

Nelson, J.R.

Baylor College of Medicine, Houston, TX
National Study Conference on Genetics, Religion,
and Ethics, 334

Nero, A.

Lawrence Berkeley Laboratory, Berkeley, CA
Air Pollutant Exposures in Buildings, 36

Newman, L.

Brookhaven National Laboratory, Upton, NY
Continental and Oceanic Fate of Energy-Related
Air Pollutants, 541

Nieman, W.C.

American Type Culture Collection, Rockville, MD
Multiplex Mapping of Human cDNAs, 330

Nierzwick-Bauer, S.A.

Rensselaer Polytechnic Institute, Troy, NY
Phylogenetic Relationships Among Subsurface
Micro-Organisms, 682

Nitsche, H.

Lawrence Berkeley Laboratory, Berkeley, CA
Experimental Investigation of Thermodynamic
Properties of Chemical Species Present in
Mixed Organic-Radionuclide Wastes, 625

Niyogi, S.K.

Oak Ridge National Laboratory, Oak Ridge, TN
Protein Engineering and Molecular Mutagenesis, 146
Protein-Nucleic Acid Interactions, 148

Nobel, P.S.

University of California, Laboratory of Biomedical
and Environmental Sciences, Los Angeles, CA
CO₂ Exchange, Environmental Productivity Indices,
and Productivity of Agave and Cacti Under Current
and Elevated Atmospheric CO₂ Concentrations, 835
Environmental Productivity Indices and Productivity
for Desert Crassulacean Acid Metabolism Plants, 711

Noordewier, M.O.

University of Wisconsin, Madison, WI
Applying Machine Learning Techniques to DNA
Sequencing Analysis, 406

Norby, L.

Oak Ridge National Laboratory, Oak Ridge, TN
Elevated Carbon Dioxide Effects on Woody Plant Soil
Systems, 828

North, G.R.

Applied Research Corporation, College Station, TX
Studies in Regional Climate Sensitivity, Predictability,
and Temporal Response, 738
Texas A&M University, College Station, TX
Signal and Noise in Global Warming Detection, 820

Novakov, T.

Lawrence Berkeley Laboratory, Berkeley, CA
Aerosol and Cloud Chemistry, 547
Modification of Cloud Optical Properties by
Aerosols, 780

Nyquist, J.E.

Oak Ridge National Laboratory, Oak Ridge, TN
Investigation of Radon Entry and Effectiveness of
Mitigation Measures, 639

Oechel, W.C.

San Diego State University, San Diego, CA
Response of Tundra Ecosystems to Elevated Atmospheric
Carbon Dioxide, 847

Oglesby, R.J.

Brown University, Providence, RI
Sensitivity of Climate Models: Comparison of Simulated
and Observed Patterns for Past Climates, 740

Ollins, D.E.

Oak Ridge National Laboratory, Oak Ridge, TN
Chromosome Chemistry, 437

Olken, F.

Lawrence Berkeley Laboratory, Berkeley, CA
Human Genome Center/Algorithms for Mapping
and Sequencing the Human Genome, 281

Olsen, A.

Lawrence Livermore National Laboratory,
Livermore, CA
Assembly, Closure, and Characterization of a
Chromosome 19 Contig Map, 292
Core Facility, 287

Olson, M.V.

University of Washington, Seattle, WA
Vertically Integrated Analysis of Human DNA, 401

Olson, T.M.

University of California, Irvine, Irvine, CA
Surface Chemistry Investigation of Colloid Transport
in Packed Beds, 656

O'Neill, R.V.

Oak Ridge National Laboratory, Oak Ridge, TN
System Processes in Landscape Ecology, 699

Orlandini, K.A.

Argonne National Laboratory, Argonne, IL
Mechanisms of Colloidal Transport in Groundwater
Environments, 614

Orpana, A.K.

University of Colorado Health Sciences Center,
Denver, CO
cDNA Sequence-Tagged Site Map of the Human
Genome: Methods Development and Applications
Using Brain cDNAs, 355

Orr, B.

University of Michigan, Ann Arbor, MI
Scanning Molecular Exciton Microscopy: A New
Approach to Gene Sequencing, 378

Osman, R.

Mount Sinai School of Medicine, New York, NY
Theoretical Studies of Molecular Mechanisms in
Radiation Damage to DNA, 200

Ostrander, E.

Lawrence Berkeley Laboratory, Berkeley, CA
Human Genome Center/High Resolution Genetic
Mapping, 283

Ott, K.C.

Los Alamos National Laboratory, Los Alamos, NM
Complementary Positron Emission Tomography and
Therapeutic Radiopharmaceuticals, 472

Overbeek, R.

Argonne National Laboratory, Argonne, IL
Computational Support for Sequence Analysis
Projects, 259

Owensby, C.E.

Kansas State University, Manhattan, KS
Rangeland-Plant Response to Elevated CO₂, 842

Pacala, S.W.

Princeton University, Princeton, NJ
A Theory of Forest Dynamics: Spatially Explicit Models
and Issues of Scale, 716

Paffenhofer, G.

Skidaway Institute of Oceanography, Savannah, GA
The Impact of Proto- and Metazooplankton on the Fate of
Organic Carbon in Continental Ocean Margins, 603

Page, G.

WNET/THIRTEEN, New York, NY
Medicine at the Crossroads, 407

Palazzolo, M.

Lawrence Berkeley Laboratory, Berkeley, CA
Human Genome Center/100 Megabase Physical
Mapping, 272
Human Genome Center/Large Scale DNA
Sequencing, 271

Palmer, C.D.

Oregon Graduate Center, Beaverton, OR
Adsorption of Chromate/Organic Acid Waste Mixtures
in Aquifer Materials, 677

Palumbo, A.V.

Oak Ridge National Laboratory, Oak Ridge, TN
Characterization and Microbial Utilization of Organic
Carbon, 635
Mixed-Waste Biodegradation, 637
Mobility of Microorganisms in a Sandy Aquifer, 636

Park, J.F.

Pacific Northwest Laboratory, Richland, WA
Inhaled Plutonium Oxide in Dogs, 73

Parks, N.J.

University of California, Davis, Davis, CA
Skeletal Remodeling Dynamics: New Approaches
with Imaging Instrumentation, 80

Parr, P.D.

Oak Ridge National Laboratory, Oak Ridge, TN
National Environmental Research Park, 701

Parrish, J.A.

Massachusetts General Hospital, Boston, MA
Center of Excellence in Laser Medicine, 510

Payne, M.G.

Oak Ridge National Laboratory, Oak Ridge, TN
Resonance Ionization Spectroscopy, 225
Vacuum Ultraviolet Ionizer Mass Spectrometer for
Genome Sequencing, 321

Peak, M.J.

Argonne National Laboratory, Argonne, IL
Cellular and Molecular Mechanisms of Radiation-
Induced DNA Damages, 109

Pearson, P.L.

The Johns Hopkins University School of Medicine,
Baltimore, MD
A Human Genome Database, 372

Pecherer, R.M.

Los Alamos National Laboratory, Los Alamos, NM
A Loosely Coupled, Distributed Laboratory Notebook
for the cDNA Community, 309

Pedersen, R.A.

University of California, San Francisco,
San Francisco, CA
Embryo Cultures and Environmental Toxicity, 120

Pelkey, J.E.

Pacific Northwest Laboratory, Richland, WA
GnomeView: A Graphical Interface to the
Human Genome, 325

Peng, T.-H.

Oak Ridge National Laboratory, Oak Ridge, TN
Oceanic Uptake of Carbon Dioxide, 856

Penner, J.E.

Lawrence Livermore National Laboratory,
Livermore, CA
Modeling in Support of DOE's Participation in the
North Atlantic Regional Experiment, 550
The Role of Aerosols and Cloud Microphysics in
Climate and Climate Change, 782

Perry, D.L.

Lawrence Berkeley Laboratory, Berkeley, CA
The Chemistry of Toxic Organic/Metal Ion
(Radionuclide) Co-Contaminants Involved
in Subsurface Transport, 626

Perry, J.S.

National Academy of Sciences, Washington, DC
Board on Atmospheric Sciences and Climate, 758

Perry, M.

Lawrence Livermore National Laboratory,
Livermore, CA
Carbon Dioxide Effects Research, 725

Peterson, E.J.

Los Alamos National Laboratory, Los Alamos, NM
Complementary Positron Emission Tomography
and Therapeutic Radiopharmaceuticals, 472
Medical Radioisotope Research Program, 473

Pfeiffer, G.P.

Beckman Research Institute, City of Hope, Duarte, CA
Improvement and Automation of Ligation-Mediated
Genomic Sequencing, 338

Phelps, T.J.

University of Tennessee, Knoxville, TN
Biochemical Markers for In Situ Microbial Community
Structure, 684
Oak Ridge National Laboratory, Oak Ridge, TN
Subsurface Microbial Ecology of GEMHEX and Triassic
Basin Samples, 638

Phillips, F.M.

New Mexico Institute of Mining and Technology,
Socorro, NM
A Geological Approach to Characterizing Aquifer
Heterogeneity, 673
Mathematical and Geological Approaches to Minimizing
the Data Requirements for Statistical Analysis of
Hydraulic Conductivity Distributions, 672

Phoenix, D.

Morehouse School of Medicine, Atlanta, GA
Impact of Technology Derived from the Human Genome
Project on Genetic Testing, Screening, and Counseling:
Cultural, Ethical, and Legal Issues, 380

Pietrafesa, L.J.

North Carolina State University, Raleigh, NC
A Study of Sediment Motions and Bottom Boundary
Layer Dynamics Over the Mid-Atlantic Bight Shelf
and Upper Slope, 595

Pilekain, C.H.

Monterey Bay Aquarium, Pacific Grove, CA
A New Instrument for Measuring Sinking Rates of
Marine Particulates In Situ, 590

Pirrung, M.C.

Duke University, Durham, NC
Preparation of Oligonucleotide Arrays for
Hybridization Studies, 363

Platt, C.M.R.

Commonwealth Scientific and Industrial Research
Organization, Mordiallac, VIC 3195 Australia
A Precise, Passive, Narrow-Beam Infrared Filter
Radiometer and Its Use with Laser Radar in the
Atmospheric Radiation Measurement Program, 359

Poeter, E.

U.S. Geological Survey, Denver, CO
Geohydrologic, Geologic, and Geochemical
Processes Affecting Radon-222 in Groundwaters
from Crystalline-Rock Aquifers, 685

Pohost, G.M.

University of Alabama, Birmingham, AL
Consortium to Develop Medical Uses of Nuclear
Magnetic Resonance Imaging, 481

Polymeropoulos, M.H.

National Institutes of Mental Health, Washington, DC
Chromosomal Localization of Brain cDNAs, 383

Pope, M.

New York University, New York, NY
Mechanisms of Interaction of Radiation with Matter, 204

Popp, R.A.

Oak Ridge National Laboratory, Oak Ridge, TN
Flow Cytometric Data Analysis, 149
Mammalian Biochemical Genetics, 56

Porch, W.M.

Los Alamos National Laboratory, Los Alamos, NM
Ocean Cloud/Climate Linkage Study, 784
Remote Sensing of Surface Fluxes Important to
Cloud Development, 783

Porter, W.P.

University of Wisconsin, Madison, WI
Physiological and Ecological Implications of Coupled
Heat-and-Water-Transport Mechanisms of
Endotherms and Vegetation, 719

Poston, J.W.

Texas A&M University, College Station, TX
Considerations of Beta and Electron Transport in
Internal Dose Calculations, 530

Prakash, L.

University of Rochester School of Medicine,
Rochester, NY
Excision Repair of Ultra-Violet Damaged DNA:
Genes and Proteins of Yeast and Humans, 176

Pratt, S.T.

Argonne National Laboratory, Argonne, IL
Highly Selective Probes of Molecular Photophysics
and Photochemistry, 208

Prell, W.L.

Brown University, Providence, RI
Sensitivity of Climate Models: Comparison of Simulated
and Observed Patterns for Past Climates, 740

Press, O.W.

University of Washington Cancer Center, Seattle, WA
Improved Radioimmunotherapy of Hematologic
Malignancies, 533

Raabe, O.G.

University of California, Davis, Davis, CA
Comparative Toxicity of Strontium-90 and Radium-226
in Beagle Dogs, 81

Radeka, V.

Brookhaven National Laboratory, Upton, NY
Biophysical Instrumentation Research, 423

Radparver, M.

Hypres, Inc., Elmsford, NY
Imaging Systems for Biomedical Applications, 506

- Radsplinner, D.A.**
University of Arizona, Tucson, AZ
Single-Molecule Detection Using Charge Coupled Device Array Technology, 331
- Raju, M.R.**
Los Alamos National Laboratory, Los Alamos, NM
Dosimetry and Cell Killing, 50
Radiobiology of Ultrasoft X Rays, 181
- Ramakrishnan, V.**
Brookhaven National Laboratory, Upton, NY
Structural Studies on Chromatin and Ribosomes, 414
- Ramanathan, V.**
Scripps Institution of Oceanography, La Jolla, CA
Atmospheric Radiation Measurement Tropical Pacific Experiment: Role of Cloud, Water Vapor and Convection Feedbacks in the Coupled Ocean/Atmosphere System, 816
Central Equatorial Pacific Experiment, 866
- Ramsey, R.S.**
Oak Ridge National Laboratory, Oak Ridge, TN
Detection of Luminescence from Lanthanide Ions as Labels for DNA Sequencing, 314
- Randall, D.A.**
Colorado State University, Fort Collins, CO
Development of an Advanced Finite-Difference Atmospheric General Circulation Model, 746
Parameterizations in High Resolution Isopycnal Wind-Driven Ocean Models, 744
The Role of Clouds in Carbon Dioxide-Induced Climate Change, 745
The Use of Atmospheric Radiation Measurement Data to Test an Improved Parameterization of Upper Tropospheric Clouds for Use in Climate Models, 801
- Rao, V.B.**
The Catholic University of America, Washington, DC
A Bacteriophage T4 In Vitro DNA Packaging System to Clone Long DNA Molecules, 350
- Rasmussen, R.A.**
Oregon Graduate Institute of Science and Technology, Beaverton, OR
Methane Fluxes from Rice Fields in China: Spatial and Temporal Variability and Estimates of Contributions to the Global Budget, 767
- Ratliff, R.L.**
Los Alamos National Laboratory, Los Alamos, NM
Genome Organization and Function, 306
- Rawson, S.A.**
Pacific Northwest Laboratory, Richland, WA
Deep Microbiology Geosciences Testing, 649
- Reba, R.C.**
University of Chicago, Chicago, IL
Development of Gamma-Emitting, Receptor Binding Radiotracers for Imaging Brain and Pancreas, 501
- Reed, D.T.**
Argonne National Laboratory, Argonne, IL
Application of High-Sensitivity Laser Techniques to Actinide Speciation in Groundwater Systems, 613
- Reeves, R.H.**
Florida State University, Tallahassee, FL
Phylogenetic Diversity Analysis of Deep Subsurface Micro-Organisms, 661
- Reilly, P.**
Eunice Kennedy Shriver Center for Mental Retardation, Waltham, MA
Genetic Data and Privacy: A Search for Model Legislation, 365
- Reimer, G.M.**
U.S. Geological Survey, Reston, VA
Gas Transport in Soils and Its Relation to Radon Availability: Identifying Regional Controls of Radon Availability, 687
- Reiner, A.**
Cold Spring Harbor Laboratory, Cold Spring Harbor, NY
A Computer System for Access to Distributed Genome Mapping Data, 352
- Repeta, D.J.**
Woods Hole Oceanographic Institution, Woods Hole, MA
Characterization of Macromolecular Components of Particulate, Colloidal, and Dissolved Organic Matter at the Sediment-Water Interface: Implications for Organic Matter Degradation Versus Preservation During Early Diagenesis in Shelf Sediments, 611
- Resnick, M.**
Los Alamos National Laboratory, Los Alamos, NM
Genetic Analysis of Yeast Artificial Chromosome Following Yeast Transformation and Mitotic Growth, 303
- Reynolds, J.F.**
Duke University, Durham, NC
Effects of Disturbances on Ecosystem Dynamics of Tundra and Riparian Vegetation, 714
Modeling the Response of Plants and Ecosystems in CO₂ and Climate Change, 837
- Rhodes, W.C.**
Florida State University, Tallahassee, FL
Selective Excitation, Relaxation, and Energy Channeling in Molecular Systems, 198
- Richards, J.F.**
Duke University, Durham, NC
Spatial and Temporal Patterns of Biotic Exchanges of CO₂ Between the Atmosphere and Tropical Landscapes and their Role in the Global Carbon Balance, 839

Richardson, C.C.

Harvard Medical School, Boston, MA
Thioredoxin-Gene 5 Protein Interactions: Processivity of Bacteriophage T7 DNA Polymerase, 367

Riggs, A.D.

Beckman Research Institute, City of Hope, Duarte, CA
Improvement and Automation of Ligation-Mediated Genomic Sequencing, 338

Rinchik, E.M.

Oak Ridge National Laboratory, Oak Ridge, TN
Generating a Comparative Physical Map of Mouse Chromosome 7, 319
Mammalian Genetics, 57
Mapping in Mouse-Human Homologous Regions, 318
Molecular Analysis of Mouse Mutations, 150

Rine, J.D.

Lawrence Berkeley Laboratory, Berkeley, CA
Human Genome Center, 265

Ringelberg, D.B.

University of Tennessee, Knoxville, TN
Biochemical Markers for In Situ Microbial Community Structure, 684

Ritchie, R.H.

Oak Ridge National Laboratory, Oak Ridge, TN
Microdosimetry, Biological Modeling, and Theoretical Biophysics, 188
Transport and Surface Physics, 190

Rittmann, B.E.

University of Illinois, Urbana, IL
Fundamental Quantitative Analysis of Microbial Activity in Aquifer Bioreclamation, 665

Robbins, E.S.

New York University Medical Center, New York, NY
Cellular Morphometry of the Bronchi of Human and Dog Lungs, 95

Robbins, R.J.

The Johns Hopkins University School of Medicine, Baltimore, MD
A Human Genome Database, 372

Robinson, D.L.

Los Alamos National Laboratory, Los Alamos, NM
Systematic Generation of Chromosome 5 Specific Sequence-Tagged Sites, 301

Robock, A.

University of Maryland, College Park, MD
Volcanic Signal in Global Change, 754

Rogers, L.E.

Pacific Northwest Laboratory, Richland, WA
Dynamics of Arid Land Ecosystems, 703
Environmental Research Park, 704

Rorschach, H.E.

Rice University, Houston, TX
Quasi-Elastic Neutron-Scattering Studies of Protein Dynamics, 443

Rose, A.W.

Pennsylvania State University, University Park, PA
Generation and Mobility of Radon in Soil, 679

Rosse, C.

University of Washington, Seattle, WA
Modulation of Lymphopoiesis, 178

Rossington, C.S.

Lawrence Berkeley Laboratory, Berkeley, CA
Semiconductor X-Ray Detectors for Synchrotrons, 221

Rothman, S.S.

Lawrence Berkeley Laboratory, Berkeley, CA
Application of X-Ray Microscopy To Study Protein Secretion, 424

Roughgarden, J.

Stanford University, Stanford, CA
Theoretical Ecology of Marine Populations, 717

Rouhi, S.

University of California, San Diego, La Jolla, CA
Symmetric Truncation of the Shallow Water Equations, 742

Rowley, J.D.

University of Chicago Medical Center, Chicago, IL
Correlation of Chromosome Patterns in Leukemic Cells of Patients with Exposure to Chemicals and/or Radiation, 166

Rubenstein, E.

Stanford University School of Medicine, Stanford, CA
K-Edge Subtraction Angiography with Synchrotron X-Rays, 525

Rudd, C.

SRI International, Menlo Park, CA
Analysis of Gene-Specific DNA Adduction by Energy-Related Chemicals, 101

Russell, B.F.

Golder Associates, Inc., Richland, WA
Drilling and Sampling Technology Research, 663

Russell, C.E.

University of Nevada, Las Vegas, NV
Spatial Variability of Deep Subsurface Micro-Organisms and Correlation with Hydrogeologic Parameters, 670

Russell, L.B.

Oak Ridge National Laboratory, Oak Ridge, TN
Freezing Mouse Mutants, 58
Mammalian Chemical Mutagenesis Program, 55
Mammalian Genetics, 57
Mapping in Mouse-Human Homologous Regions, 318

Saccomanno, G.

St. Mary's Hospital and Medical Center, Grand Junction, CO
Early Lung Cancer Detection in Uranium Miners with Abnormal Sputum Cytology, 102

Sachleben, R.A.

Oak Ridge National Laboratory, Oak Ridge, TN
Detection of Luminescence from Lanthanide Ions as
Labels for DNA Sequencing, 314
DNA Sequence Analysis by Solid-Phase
Hybridization, 316
DNA Sequencing Using Stable Isotopes, 317

Samet, J.M.

University of New Mexico School of Medicine,
Albuquerque, NM
Lung Cancer Epidemiology in New Mexico Uranium
Miners, 93
Lung Cancer in Uranium Miners—A Tissue Resource, 94

Santachi, P.

Texas A&M University, Galveston, TX
The Production of Colloids in the Benthic Boundary
Layer and Particle-Particle Interactions, 606

Sarmiento, J.L.

Princeton University, Princeton, NJ
Simulations of the Carbon Cycle in the Oceans, 846

Satyamurthy, N.

University of California, Laboratory of Biomedical
and Environmental Sciences, Los Angeles, CA
Nuclear Medicine Applications: Cyclotron, 496

Sauers, I.

Oak Ridge National Laboratory, Oak Ridge, TN
Physics of Solids and Macromolecules, 182

Saunders, E.

Los Alamos National Laboratory, Los Alamos, NM
Construction and Characterization of Human Genomic
Yeast Artificial Chromosome Library with a Low
Frequency of Chimeric Clones, 308

Saylor, G.S.

University of Tennessee, Knoxville, TN
On-Line Monitoring of Aerobic Bioremediation with
Bioluminescent Reporter Microbes, 683

Schelbert, H.R.

University of California, Laboratory of Biomedical
and Environmental Sciences, Los Angeles, CA
Nuclear Medicine Applications: Cardiovascular
Sciences, 497

Schell, D.M.

University of Alaska, Fairbanks, AK
Carbon and Nitrogen Isotope Studies in an Arctic
Ecosystem, 709

Scherer, S.

Lawrence Berkeley Laboratory, Berkeley, CA
Human Genome Center/Distribution of DNA Sequences
as Signals of Origin, 284

Schery, S.D.

New Mexico Institute of Mining and Technology,
Socorro, NM
Transport of Radon and Thoron at the Earth's
Surface, 675

Schiffer, M.

Argonne National Laboratory, Argonne, IL
Protein Structure and Conformation, 408

Schimmel, D.

University Corporation for Atmospheric Research,
Boulder, CO
Climate System Modeling Program, 773

Schimmel, J.

University of Alaska, Fairbanks, AK
Controls Over Nutrients Flow Through Plants and
Microbes in Arctic Tundra, 707

Schlmke, R.N.

University of Kansas Medical Center, Kansas City, KS
Human Genetics Education for Middle and Secondary
Science Teachers, 373

Schlemper, E.O.

University of Missouri, Columbia, MO
Bifunctional Chelates of Rh⁻¹⁰⁵ and Au⁻¹⁹⁹ as Potential
Radiotherapeutic Agents, 516

Schlesinger, M.E.

University of Illinois, Urbana, IL
Greenhouse Gas-Induced Climate Change, 750

Schlyer, D.J.

Brookhaven National Laboratory, Upton, NY
A Regional Cyclotron-Positron Emission Tomography
Center for Radiotracer Research and Medical
Application, 447

Schmitt, E.

Massachusetts Institute of Technology, Cambridge, MA
Robust Detailed Mapping of the Human Genome, 377

Schneider, D.K.

Brookhaven National Laboratory, Upton, NY
Instrumentation Development for Neutron and
Synchrotron Radiation Studies of Biological
Systems, 415

Schneider, R.P.

Pacific Northwest Laboratory, Richland, WA
Mutation of DNA Targets, 74

Schoenborn, B.P.

Brookhaven National Laboratory, Upton, NY
Study of Biological Structures by Neutron
Diffraction, 416

Schor, P.

Los Alamos National Laboratory, Los Alamos, NM
Construction and Characterization of Human Genomic
Yeast Artificial Chromosome Library with a Low
Frequency of Chimeric Clones, 308

Schultz, P.

Lawrence Berkeley Laboratory, Berkeley, CA
Catalytic Antibodies, 429
Center for Biomolecular Design, 125

Schwaiger, M.

University of Michigan Medical Center, Ann Arbor, MI
Noninvasive Evaluation of the Cardiac Autonomic
Nervous System by Positron Emission Tomography,
515

Schwartz, J.L.

Argonne National Laboratory, Argonne, IL
Analysis of DNA Damage and Mutation Induced by
Radon Daughter Products, 9
Radiation-Induced Changes in Mammalian Cells, 8

Schwartz, S.E.

Brookhaven National Laboratory, Upton, NY
Cloud Albedo Perturbations on Climate, 777

Scott, M.

Pacific Northwest Laboratory, Washington, DC
Resource Analysis Research, 830

Searls, D.B.

University of Pennsylvania, Philadelphia, PA
Foundation for a Syntactic Pattern Recognition System for
Genomic DNA Sequences, 388

Seed, T.M.

Argonne National Laboratory, Argonne, IL
Hematopoiesis in Chronic Toxicity Studies, 10

Sega, G.A.

Oak Ridge National Laboratory, Oak Ridge, TN
Mammalian Chemical Mutagenesis Program, 55

Segebrecht, L.

University of Kansas Medical Center, Kansas City, KS
Human Genetics Education for Middle and Secondary
Science Teachers, 373

Selby, P.B.

Oak Ridge National Laboratory, Oak Ridge, TN
Genetics Hazards of Radiation, 59
Mammalian Genetics, 57

Seltzer, S.

National Institute of Standards and Technology,
Gaithersburg, MD
Electron Transport Calculations with Biomedical and
Environmental Applications, 202

Semtner, A.J.

Naval Postgraduate School, Monterey, CA
Scientific Development of a Massively Parallel Ocean
Climate Model, 765

Senum, G.I.

Brookhaven National Laboratory, Upton, NY
Advancements in Atmospheric Tracers and Related
Instrumentation, 209

Setlow, R.B.

Brookhaven National Laboratory, Upton, NY
DNA Repair, Cytogenetics, and Epidemiology, 14
Radiation and Chemical Damage to DNA and Its
Repair, 114

Sevilla, M.D.

Oakland University, Rochester, MI
Mechanisms for Radiation Damage in DNA, 98

Sextro, R.G.

Lawrence Berkeley Laboratory, Berkeley, CA
Characterization of Airborne Radon Concentrations, 219
Experimental and Theoretical Investigations of Radon
Availability, Migration, and Entry, 623

Shapiro, L.P.

University of Oregon, Charleston, OR
Controls on Marine Carbon Fluxes via Phytoplankton:
Microzooplankton Interactions in Continental Shelf
Waters, 599

Shavlik, J.W.

University of Wisconsin, Madison, WI
Applying Machine Learning Techniques to DNA
Sequencing Analysis, 406

Shaw, W.J.

Pacific Northwest Laboratory, Richland, WA
Interactions Between Surface Exchange Processes and
Atmospheric Circulations, 560

Shera, E.B.

Los Alamos National Laboratory, Los Alamos, NM
Rapid DNA Sequencing Based on Fluorescence Detection
of Single Molecules, 302

Shera, K.

Los Alamos National Laboratory, Los Alamos, NM
Construction and Characterization of Human Genomic
Yeast Artificial Chromosome Library with a Low
Frequency of Chimeric Clones, 308

Sherr, B.F.

Oregon State University, Corvallis, OR
Controls on Marine Carbon Fluxes via Phytoplankton:
Microzooplankton Interactions in Continental Shelf
Waters, 599

Shizuya, H.

California Institute of Technology, Pasadena, CA
Developing a Physical Map of Human Chromosome 22
Using Pulse Alternating Current Electrophoresis and
Large Fragment Cloning, 348

Siciliano, M.J.

University of Texas, Houston, TX
Sequence Tagged Sites for Human Chromosome 19
cDNAs, 395

Siegel, D.I.

Syracuse University, Syracuse, NY
Mechanisms Controlling the Production and Transport
of Methane, Carbon Dioxide And Dissolved Solutes
Within a Large Boreal Peat Basin, 819

Siegenthaler, U.

University of Bern, CH-3012 Bern, Switzerland
Simulations of the Carbon Cycle in the Oceans, 834

Sikela, J.M.

University of Colorado Health Sciences Center,
Denver, CO
cDNA Sequence-Tagged Site Map of the Human
Genome: Methods Development and Applications
Using Brain cDNAs, 355

Sikov, M.R.

Pacific Northwest Laboratory, Richland, WA
Fetal and Juvenile Radiotoxicity, 75

Silliman, S.E.

University of Notre Dame, Notre Dame, IN
Hydrodynamic Controls on Particle Transport Through
Heterogeneous Porous Media, 676

Simmons, C.S.

Pacific Northwest Laboratory, Richland, WA
Subsurface Organic Fluid Flow, 652

Simon, M.I.

California Institute of Technology, Pasadena, CA
Developing a Physical Map of Human Chromosome 22
Using Pulse Alternating Current Electrophoresis and
Large Fragment Cloning, 348

Sims, C.S.

Oak Ridge National Laboratory, Oak Ridge, TN
Radiation Calibration Laboratory, 227

Sincovec, R.F.

Oak Ridge National Laboratory, Oak Ridge, TN
Biostatistics and Biomathematics, 63
Computational Support for Parallel Climate
Modeling, 735

Sisterson, D.L.

Argonne National Laboratory, Argonne, IL
Atmospheric Chemicals' Sources and Fates, 539

Skinner, D.M.

Oak Ridge National Laboratory, Oak Ridge, TN
Growth and Regeneration in a Land Crab Model
System, 151

Skole, D.L.

University of New Hampshire, Durham, NH
Spatial and Temporal Patterns of Biotic Exchanges
of CO₂ Between the Atmosphere and Tropical
Landscapes and Their Role in the Global
Carbon Balance, 845

Slatkin, D.N.

Brookhaven National Laboratory, Upton, NY
Physiological Targeting of Stable and Radioactive
Isotopes to Tumor for Radiotherapy, 453

Slezak, T.

Lawrence Livermore National Laboratory,
Livermore, CA
Computational Support for the Human Genome
Center: Statistical and Mathematical Analysis,
Data Processing, and Databasing, 286

Slinn, W.G.N.

Pacific Northwest Laboratory, Richland, WA
Parameterizations for Integrals of Radiation's Effects
on Clouds, Surfaces, and Stabilities, 795

Small, G.J.

Ames Laboratory, Ames, IA
Laser-Based Studies of DNA Damage and Chemical
Carcinogenesis, 207

Smith, C.L.

Boston University, Boston, MA
Physical Structure of Human Chromosome 21, 341

Smith, G.

Brookhaven National Laboratory, Upton, NY
Biophysical Instrumentation Research, 423

Smith, L.M.

University of Wisconsin, Madison, WI
Automation of the Front End of DNA Sequencing, 403
High Speed Automated DNA Sequencer, 405
High Speed DNA Sequence Analysis by Matrix-Assisted
Laser Desorption Mass Spectrometry, 404

Smith, M.H.

Savannah River Ecology Laboratory, Aiken, SC
National Environmental Research Park, 706

Smith, R.D.

Los Alamos National Laboratory, Los Alamos, NM
Massively Parallel Global Ocean Modeling, 733
Pacific Northwest Laboratory, Richland, WA
Capillary Electrophoresis Mass Spectrometry for
DNA Adducts, 234
Ion Cyclotron Resonance Mass Spectroscopy of
DNA Molecular Ions, 324

Smith, S.L.

Brookhaven National Laboratory, Upton, NY
Food Chain Dynamics, 578

Smith, W.L.

University of Wisconsin - Madison, Madison, WI
Atmospheric Radiation Measurement Fourier Transform
Spectrometer Data Analysis Tools, 821

Snyder, F.

Oak Ridge Institute for Science and Education,
Oak Ridge, TN
Alterations in Lipid Metabolism, Cell Mediators, and
Membranes in Disease, 142

Soares, M.B.

Columbia University, New York, NY
Chromosome Specific cDNAs and Sequence-Tagged
Sites, 357

Socolow, R.H.

Princeton University, Princeton, NJ

Exposure to Radon and Radon Progeny in the Indoor Environment, 251

Soderlund, C.

Los Alamos National Laboratory, Los Alamos, NM

Construction of Restriction Maps Using Simulated and Real Data, 310

Soderlund, C.A.

The Institute for Genomic Research, Gaithersburg, MD

Identification of Genes in Anonymous DNA Sequences, 369

Soloway, A.H.

Ohio State University, Columbus, OH

Synthesis and Evaluation of Boron Compounds for Neutron Capture Therapy of Malignant Brain Tumors, 519

Som, P.

Brookhaven National Laboratory, Upton, NY

Radioimmunoconjugates of Antiplatelet Monoclonal Antibodies from Thrombus Imaging, 455

Spengler, S.

Lawrence Berkeley Laboratory, Berkeley, CA

Human Genome Center/Coordinating Committee Administration, 266

Spiegelvogel, B.F.

Boron Biologicals, Inc., Raleigh, NC

Inexpensive Pathways for the Synthesis of Boronophenylalanine and New Boron-Containing Agents, 483

New Boron-Containing Amino Acids and Peptides for Boron Neutron Capture Therapy, 484

New Gadolinium-Boron Compounds for Neutron Capture Therapy, 485

Novel Base Boronated Oligonucleotides for Boron Neutron Capture Therapy, 486

Spindel, R.

Scripps Institution of Oceanography, La Jolla, CA

Acoustic Global Warming Feasibility Experiment, 865

Spinhirne, J.

National Aeronautics and Space Administration, Greenbelt, MD

Cirrus and Aerosol Profiler for Radiometric Measurements, 809

Springer, D.L.

Pacific Northwest Laboratory, Richland, WA

Molecular Events During Tumor Initiation, 76

Srivastava, P.C.

Oak Ridge National Laboratory, Oak Ridge, TN

Nuclear Medicine and Biomedical Radioisotope Technology, 478

Radiolabeled Nucleoside Probes for Tumor Diagnosis, 480

Srivastava, S.C.

Brookhaven National Laboratory, Upton, NY

Positron-Labeled Monoclonal Antibodies for Positron Emission Tomography Imaging Studies, 456

Radioimmunoconjugates of Antiplatelet Monoclonal Antibodies from Thrombus Imaging, 455

Radionuclide and Radiopharmaceutical Research for Medicine, 454

Stadelnik, R.C.

University of California, Davis Medical Center, Davis, CA

Testing the Validity of a Receptor Kinetic Model via TcNGA Functional Imaging of Liver Transplant Recipients, 489

Stallings, R.L.

Los Alamos National Laboratory Life Sciences Division, Los Alamos, NM

Construction of a 1.6 Megabase Average Resolution Sequence-Tagged Site Map of Human Chromosome 16, 297

Construction of a Cosmid, Yeast Artificial Chromosome, and Sequence-Tagged Site Physical Map of Human Chromosome 16, 299

Stamnes, K.

University of Alaska, Fairbanks, AK

The Effect of Cloud Microphysics on Climate Sensitivity, 798

Stampfer, M.R.

Lawrence Berkeley Laboratory, Berkeley, CA

Rapid Transformation Assay: Induction and Detection of In Vitro Transformation of Human Mammary Epithelial Cells, 42

Stanton, A.C.

Southwest Sciences, Inc., Santa Fe, NM

Fast Response Instrumentation for Methane Flux Measurements, 569

Fast Response Instrumentation for Methane Flux Measurements, 254

Stephens, G.L.

Brookhaven National Laboratory, Upton, NY

Radiative Properties of Nonuniform Clouds, 778

Stevens, A.

Oak Ridge National Laboratory, Oak Ridge, TN

Protein-Nucleic Acid Interactions, 148

Stevens, T.J.

University of Colorado Health Sciences Center, Denver, CO

cDNA Sequence-Tagged Site Map of the Human Genome: Methods Development and Applications Using Brain cDNAs, 355

Stewart, H.B.

Brookhaven National Laboratory, Upton, NY

Loosely Coupled Distributed Modeling of Climate Change, 721

- Stiegler, G.L.**
Pacific Northwest Laboratory, Richland, WA
Oncogenes in Radiation Carcinogenesis, 77
- Stinnett, D.B.**
Oak Ridge National Laboratory, Oak Ridge, TN
Human Genome Management Information System, 322
- Stokes, G.M.**
Pacific Northwest Laboratory, Richland, WA
Atmospheric Radiation Measurement Program, 790
- Stone, A.T.**
The Johns Hopkins University, Baltimore, MD
Release of Oxide-Bound Toxic Metals by Naturally Occurring and Contaminant-Derived Organic Compounds: The Role of Complexant, Reductant, and Adsorptive Characteristics, 666
- Stormberg, G.J.**
Idaho National Engineering Laboratory, Idaho Falls, ID
Deep Subsurface Sample Analysis at Idaho National Engineering Laboratory, 621
- Strain, B.R.**
Duke University, Durham, NC
Integration of Experimental and Modeling Approaches in the Unmanaged Ecosystem Research Plan, 838
- Strausbaugh, L.D.**
University of Connecticut, Storrs, CT
A Probe-Based Mapping Strategy for DNA Sequencing with Mobile Primers, 362
- Strauss, B.**
University of Chicago, Chicago, IL
Factors Affecting Mutational Specificity Induced by Ionizing Radiation and Oxidizing Radicals, 165
- Strelle, G.P.**
Pacific Northwest Laboratory, Richland, WA
Intermediate Scale Subsurface Transport of Co-Contaminants, 653
- Strniste, G.F.**
Los Alamos National Laboratory, Los Alamos, NM
Mechanisms of Radiation and Chemical Genetic Toxicology, 139
- Stubbs, L.J.**
Oak Ridge National Laboratory, Oak Ridge, TN
Generating a Comparative Physical Map of Mouse Chromosome 7, 319
Mapping in Mouse-Human Homologous Regions, 318
- Studler, F.W.**
Brookhaven National Laboratory, Upton, NY
Large Scale DNA Sequencing with a Primer Library, 262
Nucleic Acid Structure, 115
Rapid Preparation of DNA for Automated Sequencing, 260
Structural Biology Initiative, 417
- Stull, R.B.**
University of Wisconsin, Madison, WI
Parameterization of General Circulation Model Subgrid Nonprecipitating Cumulus and Stratocumulus Clouds Using Stochastic/Phenomenological Methods, 822
- Suokewer, S.**
Princeton University School of Engineering and Applied Science, Princeton, NJ
Reflection Imaging X-Ray Laser Microscope and Its Biological Applications, 252
- Sun, T.Q.**
University of North Carolina, Chapel Hill, NC
Development of Human Viral-Based Genomic Library of 150 to 200 Kb Inserts, 386
- Sutherland, B.M.**
Brookhaven National Laboratory, Upton, NY
DNA Repair, 116
New Approaches to DNA Mapping: Synthetic Endonucleases, 263
- Sutherland, G.R.**
Los Alamos National Laboratory, Los Alamos, NM
Construction of a Cosmid, Yeast Artificial Chromosome, and Sequence-Tagged Site Physical Map of Human Chromosome 16, 299
- Sutherland, G.R.**
Adelaide Children's Hospital, North Adelaide, South Australia 5006 Australia
Correlation of Physical and Genetic Maps of Human Chromosome 16, 326
- Sutherland, J.C.**
Brookhaven National Laboratory, Upton, NY
Synchrotron Ultraviolet User Facility, 419
Ultraviolet Radiation Damage to DNA, 418
- Sweet, R.M.**
Brookhaven National Laboratory, Upton, NY
Protein Crystallography by Synchrotron Radiation, 420
- Swift, D.L.**
The Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD
Regional Aerosol Deposition in Human Upper Airways, 90
- Swissheim, J.**
Sandia National Laboratory, Albuquerque, NM
Parallel Methods for Climate Modeling, 737
- Szecsady, J.E.**
Pacific Northwest Laboratory, Richland, WA
Intermediate Scale Subsurface Transport of Co-Contaminants, 653
- Tabor, S.**
Harvard Medical School, Boston, MA
Thioredoxin-Gene 5 Protein Interactions: Processivity of Bacteriophage T7 DNA Polymerase, 367

- Takahashi, T.**
Columbia University, Palisades, NY
CO₂ Measurements Along the World Ocean Circulation Experiment P-16 and 19 Sections in the South Pacific Ocean: A Joint Lamont-Doherty Geological Observatory/Woods Hole Oceanographic Institution Program, 859
Development of Gas Chromatographic System for Dissolved Organic Carbon Analysis in Seawater, 581
Measurements of Carbon Dioxide in the Southern Ocean Along the World Ocean Circulation Experiment S-4 Section, 860
- Talmage, J.E.**
Comstock, Inc., Oak Ridge, TN
Detection of Atmospheric Pollutants Using Infrared Lasers Produced by Stimulated Electron Raman Scattering, 564
Detection of Atmospheric Pollutants Using Infrared Lasers Produced by Stimulated Electron Raman Scattering, 239
- Tang, I.N.**
Brookhaven National Laboratory, Upton, NY
Aerosol Chemistry and Dynamics, 545
- Taylor, C.D.**
Woods Hole Oceanographic Institution, Woods Hole, MA
Moored Instrument for Time-Series Studies of Primary Production and Other Microbial Rate Processes, 608
- Taylor, E.J.**
Farachem Technology, Inc., Springfield, OH
Field-Portable Instrumentation for Metal Analysis, 240
Field-Portable Instrumentation for Metal Analysis, 660
- Taylor, K.E.**
Lawrence Livermore National Laboratory, Livermore, CA
Carbon Dioxide Effects Research, 725
- Terzaghi-Howe, M.**
Oak Ridge National Laboratory, Oak Ridge, TN
Mechanisms in Radiation Carcinogenesis, 60
The Carcinogenic Effects of Alpha-Particle Radiation on Tracheal Cells, 61
- Thakur, M.L.**
Thomas Jefferson University, Philadelphia, PA
Evaluation of Biological Response Modifiers in the Enhancement of Tumor Uptake of Tc-99m Monoclonal Antibodies, 531
- Thilly, W.G.**
Massachusetts Institute of Technology, Cambridge, MA
Mutagenesis of Human Cells In Vivo and In Vitro, 170
- Thomas, D.M.**
University of Hawaii at Manoa, Honolulu, HI
Radon Transport in the Subsurface Environment: Natural Response and Structure-Induced Effects, 664
- Thomas, J.M.**
Pacific Northwest Laboratory, Richland, WA
Designs for Environmental Field Studies, 705
- Thompson, L.H.**
Lawrence Livermore National Laboratory, Livermore, CA
Molecular Genetics of DNA Repair, 130
- Thonnard, N.**
Oak Ridge National Laboratory, Oak Ridge, TN
DNA Sequencing Using Stable Isotopes, 317
- Thundat, T.G.**
Oak Ridge National Laboratory, Oak Ridge, TN
Using Scanning Tunneling Microscopy to Sequence the Human Genome, 315
- Thurman, D.A.**
Pacific Northwest Laboratory, Richland, WA
GnomeView: A Graphical Interface to the Human Genome, 325
- Tise, J.J.**
Los Alamos National Laboratory, Los Alamos, NM
Application of a Solar-Blind LIDAR for Atmospheric and Ecological Studies, 698
- Tinoco, Jr., I.**
Lawrence Berkeley Laboratory, Berkeley, CA
Self-Processing Ribonucleic Acid, 425
University of California, Berkeley, Berkeley, CA
Structure and Stability of Nucleic Acids, 439
- Tompson, A.F.B.**
Lawrence Livermore National Laboratory, Livermore, CA
Application of Particle Methods to Multicomponent Geochemical Reactive Transport Problems, 628
- Toran, L.**
Oak Ridge National Laboratory, Oak Ridge, TN
Mixed-Waste Biodegradation, 637
- Torney, D.C.**
Los Alamos National Laboratory, Los Alamos, NM
Construction of a Cosmid, Yeast Artificial Chromosome, and Sequence-Tagged Site Physical Map of Human Chromosome 16, 299
Pooling Yeast Artificial Chromosome Libraries for Screening with Unique Sequences, 296
- Trask, B.J.**
Lawrence Livermore National Laboratory, Livermore, CA
DNA Sequence Mapping by Fluorescence In Situ Hybridization, 293
Flow and Analytical Cytogenetics, 131
National Laboratory Gene Library Project, 289
- Trebes, J.E.**
Lawrence Livermore National Laboratory, Livermore, CA
X-Ray Holography, 434

- Trewhella, J.**
Los Alamos National Laboratory, Los Alamos, NM
Biological Neutron Scattering, 435
- Trottler, R.W.**
Morehouse School of Medicine, Atlanta, GA
Impact of Technology Derived from the Human Genome
Project on Genetic Testing, Screening, and Counseling:
Cultural, Ethical, and Legal Issues, 380
- Ts'o, P.**
The Johns Hopkins University School of Hygiene
and Public Health, Baltimore, MD
Genes and Gene Expression: Localization, Damage, and
Control—A Multilevel and Interdisciplinary Study, 168
- Tucker, J.D.**
Lawrence Livermore National Laboratory,
Livermore, CA
Molecular Cytogenetics, 45
- Turekian, K.K.**
Yale University, New Haven, CT
The Determination of ^{222}Rn Flux from Soils Based on
 ^{210}Pb and ^{226}Ra Disequilibrium, 690
- Turner, J.E.**
Oak Ridge National Laboratory, Oak Ridge, TN
Microdosimetry, Biological Modeling, and Theoretical
Biophysics, 188
Pulse-Characterization Neutron Dosimetry, 228
- Turner, M.G.**
Oak Ridge National Laboratory, Oak Ridge, TN
System Processes in Landscape Ecology, 699
- Uberbacher, E.C.**
Oak Ridge National Laboratory, Oak Ridge, TN
GRAIL: An Intelligent System for DNA Sequence
Analysis, 320
Mapping in Mouse-Human Homologous Regions, 318
- Ullmann, W.J.**
University of Delaware, Lewes, DE
The Effect of Bacteria and Microbial Metabolites on
Mineral Dissolution in Subsurface Environments, 659
- Ullrich, R.L.**
University of Texas, Medical Branch at Galveston,
Galveston, TX
Cellular and Molecular Mechanisms in Radiation
Carcinogenesis, 103
- Uziel, M.**
Oak Ridge National Laboratory, Oak Ridge, TN
Dosimetry for New Energy Systems Pollutants, 229
- Valocchi, A.J.**
University of Illinois, Urbana, IL
Fundamental Quantitative Analysis of Microbial Activity
in Aquifer Bioreclamation, 665
- van den Engh, G.J.**
Lawrence Livermore National Laboratory,
Livermore, CA
Flow and Analytical Cytogenetics, 131
- Instrumentation for Cytogenetics and Gene Mapping, 294
National Laboratory Gene Library Project, 289
- Van't Hof, J.**
Brookhaven National Laboratory, Upton, NY
Eukaryotic Chromosome: Its Replication and
Structure, 117
- Vandevivere, P.**
University of Delaware, Lewes, DE
The Effect of Bacteria and Microbial Metabolites on
Mineral Dissolution in Subsurface Environments, 659
- Venter, J.C.**
The Institute for Genomic Research, Gaithersburg, MD
Expressed Sequence Tags from Human Brain cDNAs
for Genome Mapping, 370
- Vo-Dinh, T.**
Oak Ridge National Laboratory, Oak Ridge, TN
Dosimetry for New Energy Systems Pollutants, 229
- Volkert, W.A.**
University of Missouri, Columbia, MO
Production of Radiolabeled Monoclonal Antibody
Conjugates by Photoaffinity Labeling, 517
- Volkow, N.D.**
Brookhaven National Laboratory, Upton, NY
PET Research in Substance Abuse, 457
- Von Damm, K.L.**
Oak Ridge National Laboratory, Oak Ridge, TN
Radionuclides in the Coastal Zone, 702
- Vos, J.M.H.**
University of North Carolina, Chapel Hill, NC
Development of Human Viral-Based Genomic Library
of 150 to 200 Kb Inserts, 386
- Wagner, R.P.**
Los Alamos National Laboratory, Los Alamos, NM
Systematic Generation of Chromosome 5 Specific
Sequence-Tagged Sites, 301
- Wahl, G.**
Salk Institute for Biological Studies, La Jolla, CA
Isolation of Specific Human Telomeric Clones by
Homologous Recombination and Yeast Artificial
Chromosome Rescue, 392
- Walock, C.J.**
State University of New York at Albany, Albany, NY
Use of Cloud Observations and Mesoscale Meteorology
Models to Evaluate and Improve Cloud
Parameterizations, 818
- Walker, D.A.**
University of Colorado, Boulder, CO
Landscape Dynamics in the Arctic Foothills:
Landscape Evolution and Vegetation Succession
on Disturbances, 712
- Walker, D.I.**
Associated Western Universities, Salt Lake City, UT
Cooperative Research Participation Program, 154

Wall, J.S.

Brookhaven National Laboratory, Upton, NY
Scanning Transmission Electron Microscope
Operation and Development, 421
Studies of Biological Structures by Scanning
Transmission Electron Microscope, 422

Wallace, D.W.R.

Brookhaven National Laboratory, Upton, NY
Inorganic Carbon Measurements for the World Ocean
Circulation Experiment—Hydrographic Program, 855

Wallace, S.S.

University of Vermont College of Medicine,
Burlington, VT
An Immunological Approach to the Study of
DNA Repair, 105

Walsh, I.D.

Texas A&M University, College Station, TX
Optical Assessment of Large Marine Particles:
Development of an Imaging and Analysis System
for Quantifying Large Particle Distributions and
Fluxes, 607

Walters, R.A.

Ocean Optics, Inc., Dunedin, FL
A Multiaperture Optical System for In Situ
Measurement of the Flux and Sinking Speed of
Marine Snow Aggregates, 597

Walton, R.

Fermi National Accelerator Laboratory, Batavia, IL
Fermilab National Environmental Research Park, 693

Wang, W.-C.

State University of New York at Albany, Albany, NY
Study of Regional Climate Changes, 771

Wanty, R.

U.S. Geological Survey, Denver, CO
Geohydrologic, Geologic, and Geochemical
Processes Affecting Radon-222 in Groundwaters
from Crystalline-Rock Aquifers, 685

Warburton, D.

Columbia University Law School, New York, NY
Lawful Uses of Knowledge from the Human Genome
Project, 358

Ward, J.F.

University of California, San Diego, La Jolla, CA
Yields of Biologically Significant Damage Produced in
Mammalian DNA by Irradiation Associated with
Radon Decay, 85

Ward, R.C.

Oak Ridge National Laboratory, Oak Ridge, TN
Parallel Atmospheric Climate Model, 734

Warmack, R.J.

Oak Ridge National Laboratory, Oak Ridge, TN
Liquid and Submicron Physics, 187
Using Scanning Tunneling Microscopy to Sequence
the Human Genome, 315

Washington, W.M.

National Center for Atmospheric Research, Boulder, CO
Enhanced Research Program on the Long-Range Climatic
Effects of Increasing Atmospheric Carbon Dioxide, 761

Wasmoth, J.J.

Los Alamos National Laboratory, Los Alamos, NM
Systematic Generation of Chromosome 5 Specific
Sequence-Tagged Sites, 301

Wassom, J.S.

Oak Ridge National Laboratory, Oak Ridge, TN
Human Genome Management Information System, 322

Waterman, M.

California Institute of Technology, Pasadena, CA
Biological Information Signal Processor: Very Large
Scale Integration Solutions to Sequence Comparison
Problems, 349

Waters, L.C.

Oak Ridge National Laboratory, Oak Ridge, TN
Mutations in Shuttle Plasmids, 62

Watson, C.

Pacific Northwest Laboratory, Richland, WA
National Radiobiology Archives, 78

Watson, E.E.

Oak Ridge Institute for Science and Education,
Oak Ridge, TN
Radiopharmaceutical Internal Dose Information
Center, 476

Weatherly, G.L.

Florida State University, Tallahassee, FL
Numerical Studies of Bottom Boundary Layer Processes
Along the Continental Margin, 584

Webb, R.H.

Schepens Eye Research Institute, Boston, MA
Center of Excellence—Microlaser Microscope, 522

Webb, III, T.

Brown University, Providence, RI
Sensitivity of Climate Models: Comparison of Simulated
and Observed Patterns for Past Climates, 740

Weber, D.A.

Brookhaven National Laboratory, Upton, NY
Medical Applications of Nuclear Technology, 458

Weinstein, H.

Mount Sinai School of Medicine, New York, NY
Theoretical Studies of Molecular Mechanisms in
Radiation Damage to DNA, 200

Weinstein-Lloyd, J.B.

State University of New York, Old Westbury, NY
Atmospheric Peroxides, 571

Weiss, R.

University of Utah, Salt Lake City, UT
Advanced Sequencing Technology, 399

Weiss, R.R.

Scripps Institution of Oceanography, La Jolla, CA
Measurements of Surface Ocean Carbon Dioxide
Partial Pressure During World Ocean
Circulation Experimentation, 867

Welch, M.J.

Washington University School of Medicine,
St. Louis, MO
Labeling of Receptor Ligands and Other Compounds
with Halogen Radionuclides, 534
Preparation of Radiopharmaceuticals Labeled with
Gallium and Indium, 535

Welch, S.A.

University of Delaware, Lewes, DE
The Effect of Bacteria and Microbial Metabolites on
Mineral Dissolution in Subsurface Environments, 659

Wemmer, D.

Lawrence Berkeley Laboratory, Berkeley, CA
Biomolecular Structure Analysis by Nuclear
Magnetic Resonance, 430
Catalytic Antibodies, 429
Self-Processing Ribonucleic Acid, 425

Werb, Z.

University of California, San Francisco,
San Francisco, CA
Biochemical Functions of Macrophages in Pulmonary
Damage from Environmental Pollutants, 121

Wesely, M.L.

Argonne National Laboratory, Argonne, IL
Atmosphere-Ocean Chemical Exchange, 540
Atmospheric Boundary Layer Transport and Dispersion
Studies, 536
Atmospheric Chemicals' Sources and Fates, 539
Continental Dry Air-Surface Exchange, 538

Wessel, J.E.

The Aerospace Corporation, Los Angeles, CA
Molecular Detection Using Rydberg, Autoionizing,
and Cluster States, 235

West, R.

National Science Foundation, Washington, DC
University National Oceanographic Laboratory
System, 593

Westbrook, E.M.

Argonne National Laboratory, Argonne, IL
Biomedical Beamlines for APS Synchrotron, 410
Charged Coupled Device Area Detectors for
Synchrotron X Rays, 409

Wharton, R.A.

University of Nevada, Las Vegas, NV
Spatial Variability of Deep Subsurface Micro-Organisms
and Correlation with Hydrogeologic Parameters, 670

Wharton, W.

Los Alamos National Laboratory, Los Alamos, NM
Regulation of Mammalian Cell Proliferation, 140

Wheeler, K.T.

Wake Forest University Bowman Gray School of
Medicine, Winston-Salem, NC
Direct Assays of Radiation-Induced DNA Base
Lesions, 106

White, A.B.

Los Alamos National Laboratory, Los Alamos, NM
Computer Hardware, Advanced Mathematics, and
Model Physics CM-5 Support, 730

White, D.C.

University of Tennessee, Knoxville, TN
Biochemical Markers for In Situ Microbial
Community Structure, 684
On-Line Monitoring of Aerobic Bioremediation
with Bioluminescent Reporter Microbes, 683

Whiteman, C.D.

Pacific Northwest Laboratory, Richland, WA
Coupling/Decoupling of Local and Synoptic
Circulations, 561
Photometric Studies of Clouds from an Atmospheric
Radiation Measurement Program Site, 793

Whittaker, C.

Los Alamos National Laboratory, Los Alamos, NM
Pooling Yeast Artificial Chromosome Libraries for
Screening with Unique Sequences, 296

Wiersma, R.J.

Idaho National Engineering Laboratory, Idaho Falls, ID
Boron Neutron Capture Therapy Research Program, 460

Wigley, T.M.L.

University of East Anglia, Norwich NR47TJ United
Kingdom
Detection of CO₂-Induced Climate Change, 749

Wilcox, A.S.

University of Colorado Health Sciences Center, Denver,
CO
cDNA Sequence-Tagged Site Map of the Human
Genome: Methods Development and Applications
Using Brain cDNAs, 355

Wildung, R.E.

Pacific Northwest Laboratory, Richland, WA
Chemical Desorption, Dissolution, and Partitioning, 646
Chemical Remediation Concepts: Bioremediation
Concepts, 644
Manipulation of Natural Subsurface Processes: Field
Research and Validation, 645
Microbial Sequestration and Bioaccumulation of
Radionuclides and Metals, 647

Williams, A.L.

Illinois State Water Survey, Champaign, IL
Determining the Chemical Composition of Cloud
Condensation Nuclei, 805

Williams, P.

Arizona State University, Tempe, AZ
Time-of-Flight Mass Spectrometry of DNA for Rapid
Sequence Determination, 332

Williams, T.M.

Oak Ridge National Laboratory, Oak Ridge, TN
Mobility of Microorganisms in a Sandy Aquifer, 636

Wilson, D.L.

Oak Ridge National Laboratory, Oak Ridge, TN
Investigation of Radon Entry and Effectiveness of
Mitigation Measures, 639

Wilson, V.

Oak Ridge National Laboratory, Oak Ridge, TN
Subsurface Transport Model Validation and Uncertainty
Analysis in Heterogeneous Field Soils, 632

Wilson, J.L.

New Mexico Institute of Mining and Technology,
Socorro, NM
A Geological Approach to Characterizing Aquifer
Heterogeneity, 673
Mathematical and Geological Approaches to Minimizing
the Data Requirements for Statistical Analysis of
Hydraulic Conductivity Distributions, 672
Small Scale Laboratory Studies of Flow and Transport
Phenomena in Pores and Fractures: Phase II, 674

Winograd, N.

Pennsylvania State University, University Park, PA
Characterization of Carcinogenic Materials Using Ion
Beams and Lasers, 249

Wirick, C.D.

Brookhaven National Laboratory, Upton, NY
Fast Repetition Rate Fluorometer for Making In Situ
Measurements of Primary Productivity, 580
Moored Sensing Systems, 579

Wiscombe, W.J.

National Aeronautics and Space Administration,
Greenbelt, MD
Theoretical Cloud Radiation Studies in Support of the
Atmospheric Radiation Measurements Program, 810

Witkowski, J.

Cold Spring Harbor Laboratory, Cold Spring Harbor,
NY
Human Genetics and Genome Analysis: A Practical
Workshop for Public Policymakers and Opinion
Leaders, 351

Wohlpart, A.

Oak Ridge Institute for Science and Education, Oak
Ridge, TN
Alexander Hollaender Distinguished Postdoctoral
Fellowships, 53
Human Genome Distinguished Postdoctoral Fellowships,
313
OHER/Historically Black Colleges and Universities
Faculty and Student Research Participation Program, 54

Wolf, A.P.

Brookhaven National Laboratory, Upton, NY
A Regional Cyclotron-Positron Emission Tomography
Center for Radiotracer Research and Medical
Application, 447

Wolff, S.

University of California, San Francisco,
San Francisco, CA
Elucidation of Cytogenetic Damage, 16

Wollenberg, H.A.

Lawrence Berkeley Laboratory, Berkeley, CA
Experimental and Theoretical Investigations of Radon
Availability, Migration, and Entry, 623

Woloschak, G.E.

Argonne National Laboratory, Argonne, IL
Genetic Effects of High Linear Energy Transfer
Radiation, 11
Inactivation of Cancer Suppressor Genes in Radiation-
Induced Tumors, 12

Wood, A.M.

University of Oregon, Eugene, OR
Phytoplankton Excretion Revisited: Healthy Cells May
Not Do It, But How Many Cells Are Healthy?, 598

Wood, B.D.

Pacific Northwest Laboratory, Richland, WA
Microbial Origin/Transport in Subsurface Systems, 651

Wood, C.C.

Los Alamos National Laboratory, Los Alamos, NM
Imaging Function in the Human Brain, 474

Woodbury, N.

Arizona State University, Tempe, AZ
Time-of-Flight Mass Spectrometry of DNA for Rapid
Sequence Determination, 332

Woodward, W.

Southern Methodist University, Dallas, TX
Statistical Examination of Climatological Data
Relevant to Global Temperature Variations, 817

Worgul, B.V.

Columbia University College of Physicians and
Surgeons, New York, NY
Low Dose Neutron Late Effects: Cataractogenesis, 87

Woychik, R.P.

Oak Ridge National Laboratory, Oak Ridge, TN
DNA Sequencing Using Stable Isotopes, 317
Detection of Luminescence from Lanthanide Ions as
Labels for DNA Sequencing, 314
Insertional Mutagenesis and Gene Analysis, 152
Mapping in Mouse-Human Homologous Regions, 318

Wuebbles, D.J.

Lawrence Livermore National Laboratory,
Livermore, CA
Scientific Development of the Advanced Parallel
Chemistry Climate Model, 728
Trace Gas Interactions in the Global Atmosphere, 727

Wyriek, J.M.

Oak Ridge National Laboratory, Oak Ridge, TN
Human Genome Management Information System, 322

Wyrobek, A.J.

Lawrence Livermore National Laboratory,
Livermore, CA
Detection of Gene Mutations and Chromosomal
Abnormalities in Human Sperm, 132

Yanoh, J.C.

Massachusetts Institute of Technology, Boston, MA
Accelerator-Based Epithermal Neutron Capture Therapy:
Design of Neutron Source and Irradiation Facility, 511

Yang, W.K.

Oak Ridge National Laboratory, Oak Ridge, TN
Carcinogen-Cell Genome Interaction, 153

Yeh, G.T.

Pennsylvania State University, University Park, PA
Field-Scale Validation and Development of a
Three-Dimensional Fluid Flow and Multispecies-
Hydrogeochemical Transport Model, 678

Yeh, H.-C.

Inhalation Toxicology Research Institute,
Albuquerque, NM
Biologically Relevant Properties of Energy-Related
Aerosols, 34
Deposition of Radon and Radon Progeny in the
Respiratory Tract, 35

Yeh, T.-C.J.

University of Arizona, Tucson, AZ
Stochastic Analysis of Macrodispersion in Unsaturated
Heterogeneous Porous Media, 655

Yesley, M.S.

Los Alamos National Laboratory, Los Alamos, NM
Ethical, Legal, and Social Issues Projects, 311

Yeung, E.S.

Ames Laboratory, Ames, IA
Quantitation in Electrophoresis Based on Lasers, 257

Yoshida, T.M.

Los Alamos National Laboratory, Los Alamos, NM
High Precision Mapping of Yeast Artificial Chromosome
Clones onto Chromosome 21 by Fluorescence In Situ
Hybridization and Image Analysis, 304

Yoderian, P.A.

California Institute for Biological Research, La Jolla, CA
New Hosts and Vectors for Genome Cloning, 347

Yu, J.-W.

University of Colorado Health Sciences Center,
Denver, CO
Chromosome Region-Specific Libraries for Human
Genome Analysis, 356

Yust, L.N.

Oak Ridge National Laboratory, Oak Ridge, TN
Human Genome Management Information System, 322

Zachara, J.M.

Pacific Northwest Laboratory, Richland, WA
Manipulation of Natural Subsurface Processed: Field
Research and Validation, 645
Subsurface Chemistry of Organic Chemical and Organic/
Radionuclide Mixtures, 642

Zalder, M.

Columbia University, New York, NY
Nanodosimetry and Nanodosimetric-Based Models of
Radiation Action for Radon-Alpha Particles, 238
Radiation Physics and Biology, 196

Zalutsky, M.R.

Duke University Medical Center, Durham, NC
Positron Emission Tomographic Imaging of Tumors
Using Monoclonal Antibodies, 505

Zamenhof, R.G.

Tufts-New England Medical Center, Boston, MA
A Clinical Trial of Neutron Capture Therapy for Brain
Tumors, 532

Zeman, H.D.

University of Tennessee, Memphis, TN
Intravenous Coronary Angiography Utilizing K-Emission
and Bremsstrahlung X Rays Produced by Electron
Bombardment, 526

Zika, R.G.

University of Miami, Miami, FL
Use of a Laser-Based Monitoring Technique to Measure
Trace Gas Fluxes Across the Air-Sea Interface, 807

Zorn, M.D.

Lawrence Berkeley Laboratory, Berkeley, CA
Human Genome Center/Software and Data Resource
Facility, 282

Zweig, G.

Los Alamos National Laboratory, Los Alamos, NM
Modeling of Cochlear Mechanisms, 475

Institution Index

ALEM Associates, Boston, MA**Lempicki, A.**

Improved Scintillator Materials for Medical Applications, 482

Adelaide Children's Hospital, North Adelaide, South Australia 5006 Australia**Sutherland, G.R.**

Correlation of Physical and Genetic Maps of Human Chromosome 16, 326

Advanced Technology Applications, Inc., Research Triangle Park, NC**Dettloff, W.**

Interactive DNA Sequence Processing for a Microcomputer, 327

Aerospace Corporation, The, Los Angeles, CA**Wessel, J.E.**

Molecular Detection Using Rydberg, Autoionizing, and Cluster States, 235

Affymax Research Institute, Palo Alto, CA**Fodor, S.P.A.**

Spatially Defined Oligonucleotide Arrays, 328

Alabama, University of, Birmingham, AL**Pohost, G.M.**

Consortium to Develop Medical Uses of Nuclear Magnetic Resonance Imaging, 481

Alaska, University of, Fairbanks, AK**Kane, D.L.**

Arctic Hydrology and Meteorology, 708

Schell, D.M.

Carbon and Nitrogen Isotope Studies in an Arctic Ecosystem, 709

Schimel, J.

Controls Over Nutrients Flow Through Plants and Microbes in Arctic Tundra, 707

Stamnes, K.

The Effect of Cloud Microphysics on Climate Sensitivity, 798

Alberta, University of, Edmonton, Alberta T6G 2G2 Canada**Dovichi, N.J.**

Multicolumn Gel Electrophoresis and Laser-Induced Fluorescence Detection for DNA Sequencing at 64,000 Bases/Hour, 329

American Type Culture Collection, Rockville, MD**Maglott, D.R.**

Multiplex Mapping of Human cDNAs, 330

Nierman, W.C.

Multiplex Mapping of Human cDNAs, 330

Ames Laboratory, Ames, IA**D'Silva, A.P.**

Laser-Based Studies of DNA Damage and Chemical Carcinogenesis, 207

Small, G.J.

Laser-Based Studies of DNA Damage and Chemical Carcinogenesis, 207

Yeung, E.S.

Quantitation in Electrophoresis Based on Lasers, 257

Applied Research Corporation, College Station, TX**Crowley, T.J.**

Studies in Regional Climate Sensitivity, Predictability, and Temporal Response, 738

North, G.R.

Studies in Regional Climate Sensitivity, Predictability, and Temporal Response, 738

Argonne National Laboratory, Argonne, IL**Atcher, R.W.**

Research in Nuclear Medicine, 445

Bhattacharyya, M.H.

Biochemical Mechanisms of Chemically Induced Health Effects, 1

Carnes, B.A.

Interspecies Extrapolation for Radiation-Induced Carcinogenic Risk, 2

Coulter, R.L.

Area-Representative Estimates of Surface Heat Flux for
Clouds and Radiation Testbed Sites, 776
Atmospheric Boundary Layer Transport and
Dispersion Studies, 536

Crkvenjakov, R.

An Integral Approach to Genome Studies, 258

Dehmer, P.M.

Highly Selective Probes of Molecular Photophysics
and Photochemistry, 208

Dehmer, J.L.

Highly Selective Probes of Molecular Photophysics
and Photochemistry, 208

Drmanac, R.

An Integral Approach to Genome Studies, 258

Foster, I.T.

Parallel Atmospheric Climate Model, 720

Fritz, T.E.

Radiation Toxicity Studies in Dogs for Interspecies
Comparison, 3

Gaffney, J.S.

Atmospheric Chemistry of Organic Oxidants and
Aldehydes, 537

Investigation of Organic/Inorganic Complexation
Processes in Subsurface Environments, 615

Mechanisms of Colloidal Transport in Groundwater
Environments, 614

Giometti, C.S.

Analysis of Protein Expression, 4

Grdina, D.J.

Mutagenesis and Carcinogenesis by Low Dose
Irradiation, 5

Hansen, D.K.

Structural Studies of Site-Specific Mutants of
the Photosynthetic Reaction Center, 108

Huberman, E.

Chemical Carcinogenesis Studies in Human and
Rodent Cells, 6

Oncogenes and Human Radiation Carcinogenesis, 7

Inokuti, M.

Molecular Radiation Physics, 179

Jastrow, J.D.

Cooperative Support for the Fermilab National
Environmental Research Park, 691

Marley, N.A.

Atmospheric Chemistry of Organic Oxidants and
Aldehydes, 537

Investigation of Organic/Inorganic Complexation
Processes in Subsurface Environments, 615

Mechanisms of Colloidal Transport in Groundwater
Environments, 614

Miller, R.M.

Stress Tolerance Strategies in Plant/Soil Systems, 692

Orlandini, K.A.

Mechanisms of Colloidal Transport in Groundwater
Environments, 614

Overbeek, R.

Computational Support for Sequence Analysis
Projects, 259

Peak, M.J.

Cellular and Molecular Mechanisms of Radiation-
Induced DNA Damages, 109

Pratt, S.T.

Highly Selective Probes of Molecular Photophysics
and Photochemistry, 208

Reed, D.T.

Application of High-Sensitivity Laser Techniques to
Actinide Speciation in Groundwater Systems, 613

Schiffer, M.

Protein Structure and Conformation, 408

Schwartz, J.L.

Analysis of DNA Damage and Mutation Induced by
Radon Daughter Products, 9

Radiation-Induced Changes in Mammalian Cells, 8

Seed, T.M.

Hematopoiesis in Chronic Toxicity Studies, 10

Sisterson, D.L.

Atmospheric Chemicals' Sources and Fates, 539

Wesely, M.L.

Atmosphere-Ocean Chemical Exchange, 540

Atmospheric Boundary Layer Transport and
Dispersion Studies, 536

Atmospheric Chemicals' Sources and Fates, 539

Continental Dry Air-Surface Exchange, 538

Westbrook, E.M.

Biomedical Beamlines for APS Synchrotron, 410

Charged Coupled Device Area Detectors for
Synchrotron X Rays, 409

Woleschak, G.E.

Genetic Effects of High Linear Energy Transfer
Radiation, 11

Inactivation of Cancer Suppressor Genes in
Radiation-Induced Tumors, 12

Arizona, University of, Tucson, AZ

Arnold, R.G.

Transport of Subsurface Biocolloids in Porous
Media, 654

Baker, M.E.

Single-Molecule Detection Using Charge Coupled
Device Array Technology, 331

Bales, R.C.

Transport of Subsurface Biocolloids in Porous
Media, 654

Denton, M.B.

Single-Molecule Detection Using Charge Coupled Device Array Technology, 331

Dickinson, R.E.

The Land Component of the Global Climate System with Adequate Spatial Resolution, 739

Earle, C.W.

Single-Molecule Detection Using Charge Coupled Device Array Technology, 331

Garbe, C.P.

Transport of Subsurface Biocolloids in Porous Media, 654

Keller, R.

Single-Molecule Detection Using Charge Coupled Device Array Technology, 331

Radspinner, D.A.

Single-Molecule Detection Using Charge Coupled Device Array Technology, 331

Yeh, T.-C.J.

Stochastic Analysis of Macrodispersion in Unsaturated Heterogeneous Porous Media, 655

Arizona State University, Tempe, AZ

Williams, P.

Time-of-Flight Mass Spectrometry of DNA for Rapid Sequence Determination, 332

Woodbury, N.

Time-of-Flight Mass Spectrometry of DNA for Rapid Sequence Determination, 332

Associated Western Universities, Salt Lake City, UT

Walker, D.I.

Cooperative Research Participation Program, 154

Atom Sciences, Inc., Oak Ridge, TN

Arlinghaus, H.F.

Increased Speed in DNA Sequencing by Utilizing Laser Atomization Resonance Ionization Spectroscopy and Sputter-Initiated Resonance Ionization Spectroscopy to Localize Multiple Stable Isotope Labeled Fragments, 333

Baylor College of Medicine, Houston, TX

Caskey, C.T.

Mapping and Ordered Cloning of the Human X Chromosome, 336

National Study Conference on Genetics, Religion, and Ethics, 334

Lawrence, C.

Genome Assembly Manager, 335

Nelson, D.L.

Isolation of cDNAs from the Human X Chromosome and Derivation of Related Sequence-Tagged Sites, 337

Nelson, J.R.

National Study Conference on Genetics, Religion, and Ethics, 334

Baylor College of Medicine, Institute of Religion, Houston, TX

Bouma, III, H.

National Study Conference on Genetics, Religion, and Ethics, 334

Beckman Research Institute, City of Hope, Duarte, CA

Pfeiffer, G.P.

Improvement and Automation of Ligation-Mediated Genomic Sequencing, 338

Riggs, A.D.

Improvement and Automation of Ligation-Mediated Genomic Sequencing, 338

Bern, University of, CH-3012 Bern, Switzerland

Siegenthaler, U.

Simulations of the Carbon Cycle in the Oceans, 834

BIODE, Inc., Cape Elizabeth, ME

McAllister, D.J.

An Acoustic Plate Mode DNA Biosensor, 339

Boron Biologicals, Inc., Raleigh, NC

Spielvogel, B.F.

Inexpensive Pathways for the Synthesis of Boronophenylalanine and New Boron-Containing Agents, 483

New Boron-Containing Amino Acids and Peptides for Boron Neutron Capture Therapy, 484

New Gadolinium-Boron Compounds for Neutron Capture Therapy, 485

Novel Base Boronated Oligonucleotides for Boron Neutron Capture Therapy, 486

Boston College, Chestnut Hill, MA

Davidovits, P.

Measurement of Gas-Water Uptake Coefficients for Trace Gases Active in the Marine Environment, 563

Boston University, Boston, MA

Cantor, C.R.

Overcoming Genome-Mapping Bottlenecks, 340

Lempicki, A.

Scintillation Materials for Medical Applications, 487

Smith, C.L.

Physical Structure of Human Chromosome 21, 341

Brandeis University, Waltham, MA

Haber, J.E.

Mechanisms of Repair of Double-Strand Chromosomal Breaks, 79

Brookhaven National Laboratory, Upton, NY

- Abola, E.E.**
Protein Data Bank Operations, 264
- Anderson, C.W.**
Control of Gene Expression in Mammalian Cells and Viruses, 110
- Bender, M.A.**
DNA Repair, Cytogenetics, and Epidemiology, 14
- Bond, V.P.**
Radiation Carcinogenesis Dose-Effect Relationships of Varying Energies of Neutrons in Leukemogenesis, 13
- Brooks, M.H.**
Brookhaven Medical Research Reactor Operations, 459
- Brugger, R.M.**
Joint Proposal for Neutron Capture Therapy, 448
- Capel, M.S.**
Synchrotron X-Radiation Scattering Spectrometer for the Study of Biological Structures, 411
- Coderre, J.A.**
Clinical Feasibility of Boron Neutron Capture Therapy Using p-Boronophenylalanine, 449
- Daum, P.H.**
Analysis of Aerosol Chemical and Microphysical Data in the North Atlantic Regional Experiment, 542
Continental and Oceanic Fate of Energy-Related Air Pollutants, 541
Radiative Properties of Nonuniform Clouds, 778
- Dewey, S.**
A Regional Cyclotron-Positron Emission Tomography Center for Radiotracer Research and Medical Application, 447
- Dietz, R.N.**
Advancements in Atmospheric Tracers and Related Instrumentation, 209
Atmospheric Tracer and Instrumentation Development, 543
- Dilmanian, F.A.**
Multiple Energy Computed Tomography for Neuroradiology with Monochromatic X Rays from the National Synchrotron Light Source, 450
- Dunn, J.J.**
Large Scale DNA Sequencing with a Primer Library, 262
Nucleic Acid Replication, 111
Rapid Preparation of DNA for Automated Sequencing, 260
- Falkowski, P.G.**
Coastal Productivity, 573
Diagnostic Analysis of Iron Limitation of CO₂ Uptake by Oceanic Phytoplankton, 854
Molecular Ecology of Phytoplankton Photosynthesis, 574
- Ferriest, R.F.**
A Regional Cyclotron-Positron Emission Tomography Center for Radiotracer Research and Medical Application, 447
- Flagg, C.N.**
Coastal Transport and Diffusion, 575
- Fowler, J.S.**
A Regional Cyclotron-Positron Emission Tomography Center for Radiotracer Research and Medical Application, 447
- Francis, A.J.**
Biodegradation of Selected Organic Compounds and Complexing Agents of Radionuclides and Metals, 616
Role of Micro-Organisms as Regulators of Uranium Mobility in Natural Radioactive Mineral Deposits, 617
- Gatley, J.S.**
A Regional Cyclotron-Positron Emission Tomography Center for Radiotracer Research and Medical Application, 447
- Hainfeld, J.F.**
High Resolution DNA Mapping by Scanning Transmission Electron Microscopy, 261
Radioactive Gold Clusters Bound to Tumor Antibodies for Cancer Therapy, 446
- Harbottle, G.**
Fundamental Studies of Radon Release from Soil, 618
- Hendrey, G.**
Free Air Carbon Dioxide Field Enrichment Facility Development, 823
- Hough, P.V.C.**
Transcription in Eukaryotes, 412
- Joel, D.D.**
Evaluation of Boron Compounds for Neutron Capture Therapy, 451
- Johnson, K.**
Inorganic Carbon Measurements for the World Ocean Circulation Experiment—Hydrographic Program, 855
- Kemp, P.**
Measurement of Marine Microbial Growth, 577
Microbial Processes in Coastal Marine Systems, 576
- Kleinman, L.I.**
Continental and Oceanic Fate of Energy-Related Air Pollutants, 541
Radiative Properties of Nonuniform Clouds, 778
- Koetzle, T.F.**
Protein Data Bank Operations, 264
- Lacks, S.A.**
Reactions of DNA Within Cells, 112
- Lawson, C.L.**
Structural Studies on Proteins by X-Ray Diffraction, 413

- Lee, Y.N.**
Atmospheric Organic Chemistry: Investigation of Primary and Secondary Species, 544
Continental and Oceanic Fate of Energy-Related Air Pollutants, 541
- Levy, A.**
A Regional Cyclotron-Positron Emission Tomography Center for Radiotracer Research and Medical Application, 447
- Mangel, W.F.**
The Roles of Proteases in Normal and Abnormal Physiological Processes, 113
- Mausner, L.F.**
Radioactive Gold Clusters Bound to Tumor Antibodies for Cancer Therapy, 446
- Mease, R.C.**
Synthesis of New Rigid Chelating Agents for Preparing Stable Radiometal Immunoconjugates, 452
- Newman, L.**
Continental and Oceanic Fate of Energy-Related Air Pollutants, 541
- Radeka, V.**
Biophysical Instrumentation Research, 423
- Ramakrishnan, V.**
Structural Studies on Chromatin and Ribosomes, 414
- Schlyer, D.J.**
A Regional Cyclotron-Positron Emission Tomography Center for Radiotracer Research and Medical Application, 447
- Schneider, D.K.**
Instrumentation Development for Neutron and Synchrotron Radiation Studies of Biological Systems, 415
- Schoenborn, B.P.**
Study of Biological Structures by Neutron Diffraction, 416
- Schwartz, S.E.**
Cloud Albedo Perturbations on Climate, 777
- Senum, G.I.**
Advancements in Atmospheric Tracers and Related Instrumentation, 209
- Setlow, R.B.**
DNA Repair, Cytogenetics, and Epidemiology, 14
Radiation and Chemical Damage to DNA and Its Repair, 114
- Slatkin, D.N.**
Physiological Targeting of Stable and Radioactive Isotopes to Tumor for Radiotherapy, 453
- Smith, G.**
Biophysical Instrumentation Research, 423
- Smith, S.L.**
Food Chain Dynamics, 578
- Som, P.**
Radioimmunoconjugates of Antiplatelet Monoclonal Antibodies from Thrombus Imaging, 455
- Srivastava, S.C.**
Positron-Labeled Monoclonal Antibodies for Positron Emission Tomography Imaging Studies, 456
Radioimmunoconjugates of Antiplatelet Monoclonal Antibodies from Thrombus Imaging, 455
Radionuclide and Radiopharmaceutical Research for Medicine, 454
- Stephens, G.L.**
Radiative Properties of Nonuniform Clouds, 778
- Stewart, H.B.**
Loosely Coupled Distributed Modeling of Climate Change, 721
- Studler, F.W.**
Large Scale DNA Sequencing with a Primer Library, 262
Nucleic Acid Structure, 115
Rapid Preparation of DNA for Automated Sequencing, 260
Structural Biology Initiative, 417
- Sutherland, B.M.**
DNA Repair, 116
New Approaches to DNA Mapping: Synthetic Endonucleases, 263
- Sutherland, J.C.**
Synchrotron Ultraviolet User Facility, 419
Ultraviolet Radiation Damage to DNA, 418
- Sweet, R.M.**
Protein Crystallography by Synchrotron Radiation, 420
- Tang, I.N.**
Aerosol Chemistry and Dynamics, 545
- Van't Hof, J.**
Eukaryotic Chromosome: Its Replication and Structure, 117
- Volkow, N.D.**
PET Research in Substance Abuse, 457
- Wall, J.S.**
Scanning Transmission Electron Microscope Operation and Development, 421
Studies of Biological Structures by Scanning Transmission Electron Microscope, 422
- Wallace, D.W.R.**
Inorganic Carbon Measurements for the World Ocean Circulation Experiment—Hydrographic Program, 855
- Weber, D.A.**
Medical Applications of Nuclear Technology, 458

Wirick, C.D.

Fast Repetition Rate Fluorometer for Making In Situ Measurements of Primary Productivity, 580
Moored Sensing Systems, 579

Wolf, A.P.

A Regional Cyclotron-Positron Emission Tomography Center for Radiotracer Research and Medical Application, 447

Brown University, Providence, RI

Oglesby, R.J.

Sensitivity of Climate Models: Comparison of Simulated and Observed Patterns for Past Climates, 740

Prell, W.L.

Sensitivity of Climate Models: Comparison of Simulated and Observed Patterns for Past Climates, 740

Webb, III, T.

Sensitivity of Climate Models: Comparison of Simulated and Observed Patterns for Past Climates, 740

California, University of, Berkeley, Berkeley, CA

Beeson, D.

Pathways to Genetic Screening: Patient Knowledge Patient Practices, 344

Chapin, III, F.S.

Controls Over Nutrients Flow Through Plants and Microbes in Arctic Tundra, 710

Duster, T.

Pathways to Genetic Screening: Patient Knowledge Patient Practices, 344

Glazer, A.N.

Ultrasensitive Fluorescence Detection of DNA, 342

Gusfield, D.

Efficient Algorithms and Data Structures in Support of DNA Mapping and Sequence Analysis, 343

Lawler, E.

Efficient Algorithms and Data Structures in Support of DNA Mapping and Sequence Analysis, 343

Linn, S.

Endonucleases Involved in Repair and Recombination of DNA, 155

Mathies, R.A.

Ultrasensitive Fluorescence Detection of DNA, 342

Tinoco, Jr., I.

Structure and Stability of Nucleic Acids, 439

California, University of, Cedars—Sinai Medical Center, Los Angeles, CA

Korenberg, J.R.

Human cDNA Mapping Using Fluorescence In Situ Hybridization, 345

California, University of, Davis, Davis, CA

Boyd, J.B.

Studies of the Repair of Radiation-Induced Genetic Damage in *Drosophila*, 156

Bradbury, E.M.

Neutron Scatter Studies of Chromatin, 440

Delwiche, C.C.

National Institute for Global Environmental Change, 869

Parks, N.J.

Skeletal Remodeling Dynamics: New Approaches with Imaging Instrumentation, 80

Raabe, O.G.

Comparative Toxicity of Strontium-90 and Radium-226 in Beagle Dogs, 81

California, University of, Davis Medical Center, Davis, CA

Stadainik, R.C.

Testing the Validity of a Receptor Kinetic Model via TcNGA Functional Imaging of Liver Transplant Recipients, 489

California, University of, Irvine, Irvine, CA

Ayala, F.J.

Genetic Variation in Resistance to Ionizing Radiation, 157

Berna, M.W.

A Center for Excellence for the Medical Application of Lasers, 490

Olson, T.M.

Surface Chemistry Investigation of Colloid Transport in Packed Beds, 656

California, University of, Laboratory of Biomedical and Environmental Sciences, Los Angeles, CA

Barrio, J.R.

Nuclear Medicine Applications: Chemistry/Biochemistry, 491

Chugani, D.C.

Nuclear Medicine Applications: Molecular and Cellular Biology, 492

Colicelli, J.

DNA Replication, Recombination and Repair, 158

Fulco, A.J.

Biosynthetic Control, 159

Hankinson, O.

Chemical Carcinogenesis, 83

Hays, E.F.

Hematopoietic Toxicology, 160

Herschman, H.R.

Cell Biology and Gene Expression, 161

Hoffman, E.J.

Nuclear Medicine Applications: Physical Sciences, 493

Huang, H. S.-C.

Nuclear Medicine Applications: Biomathematics, 494

Maxziotta, J.C.

Nuclear Medicine Applications: Neuroscience, 495

McEntee, K.

DNA Damage and Gene Expression, 162

Nobel, P.S.

CO₂ Exchange, Environmental Productivity Indices, and Productivity of Agave and Cacti Under Current and Elevated Atmospheric CO₂ Concentrations, 835

Environmental Productivity Indices and Productivity for Desert Crassulacean Acid Metabolism Plants, 711

Satyamurthy, N.

Nuclear Medicine Applications: Cyclotron, 496

Scheibert, H.R.

Nuclear Medicine Applications: Cardiovascular Sciences, 497

de Vellis, J.

Developmental Neurotoxicology, 82

California, University of, Los Angeles, Los Angeles, CA

Arakawa, A.

Development of an Advanced Finite-Difference Atmospheric General Circulation Model, 741

Gatti, R.A.

Genetic Localization of Ataxia Telangiectasia Gene(s): A Human Gene(s) for Radiation Sensitivity, 163

Mechoso, C.R.

Development of an Advanced Finite-Difference Atmospheric General Circulation Model, 741

California, University of, Davis, Sacramento, CA

DeNardo, S.J.

Copper-67 Lym-1 Feasibility Trial of Therapy for Lymphoma, 488

California, University of, San Diego, La Jolla, CA

Haas, M.

Comparative Studies in Mouse and Man, 84

Karin, M.

The Molecular Basis for Ultraviolet Response of Cultured Human Cells, 164

Rouhi, S.

Symmetric Truncation of the Shallow Water Equations, 742

Ward, J.F.

Yields of Biologically Significant Damage Produced in Mammalian DNA by Irradiation Associated with Radon Decay, 85

California, University of, San Francisco, San Francisco, CA

Banda, M.

Biochemical Functions of Macrophages in Pulmonary Damage from Environmental Pollutants, 121

Cleaver, J.E.

DNA Replication and Repair, 119

Mammalian Cell Culture Systems for Molecular Studies of DNA, Mutagenicity, and Carcinogenicity, 118

Mechanisms of Mutagenesis by Alpha Particles and X Rays in Human Cells, 15

Gray, J.

Molecular Cytogenetics and Computer-Assisted Microscopy, 346

Morgan, W.F.

Elucidation of Cytogenetic Damage, 16

Murnane, J.

DNA Replication and Repair, 119

Pedersen, R.A.

Embryo Cultures and Environmental Toxicity, 120

Werb, Z.

Biochemical Functions of Macrophages in Pulmonary Damage from Environmental Pollutants, 121

Wolff, S.

Elucidation of Cytogenetic Damage, 16

California, University of, San Francisco School of Pharmacy, San Francisco, CA

Kahl, S.B.

Carboranyl Amino Acids for Site-Specific Neutron Capture Therapy of Malignant Melanoma, 498

California Institute for Biological Research, La Jolla, CA

Greener, P.

New Hosts and Vectors for Genome Cloning, 347

Youderian, P.A.

New Hosts and Vectors for Genome Cloning, 347

California Institute of Technology, Pasadena, CA

Birren, B.

Developing a Physical Map of Human Chromosome 22 Using Pulse Alternating Current Electrophoresis and Large Fragment Cloning, 348

Chen, E.

Biological Information Signal Processor: Very Large Scale Integration Solutions to Sequence Comparison Problems, 349

Hood, L.E.

Biological Information Signal Processor: Very Large Scale Integration Solutions to Sequence Comparison Problems, 349

Hunkapiller, T.

Biological Information Signal Processor: Very Large Scale Integration Solutions to Sequence Comparison Problems, 349

McKoy, V.

Resonance Enhanced Multiphoton Ionization Spectra of Molecules and Molecular Spectra, 236

Shizuya, H.

Developing a Physical Map of Human Chromosome 22 Using Pulse Alternating Current Electrophoresis and Large Fragment Cloning, 348

Simon, M.I.

Developing a Physical Map of Human Chromosome 22 Using Pulse Alternating Current Electrophoresis and Large Fragment Cloning, 348

Waterman, M.

Biological Information Signal Processor: Very Large Scale Integration Solutions to Sequence Comparison Problems, 349

Case Western Reserve University, Cleveland, OH

Bakale, G.

Ionization in Liquids: Electron Transport and Reactions in Model, Biometric, and Biological Systems, 195

Evans, H.H.

Mutagenicity of Radon and Radon Daughters, 86

Catholic University of America, Washington, DC

Joshi, V.

A Bacteriophage T4 In Vitro DNA Packaging System to Clone Long DNA Molecules, 350

Rao, V.B.

A Bacteriophage T4 In Vitro DNA Packaging System to Clone Long DNA Molecules, 350

Cincinnati, University of, Cincinnati, OH

Heineman, W.R.

Development of More Efficacious Tc-99m Organ Imaging Agents, 502

Chicago, University of, Chicago, IL

Beck, R.N.

Instrumentation and Quantitative Methods of Evaluation, 499

Cooper, M.

Quantitative Studies in Radiopharmaceutical Science, 500

Crewe, A.V.

Electron Microscope Development, 441

Kapp, O.H.

Electron Microscope Development, 441

Reba, R.C.

Development of Gamma-Emitting, Receptor Binding Radiotracers for Imaging Brain and Pancreas, 501

Strauss, B.

Factors Affecting Mutational Specificity Induced by Ionizing Radiation and Oxidizing Radicals, 165

Chicago Medical Center, University of, Chicago, IL

Rowley, J.D.

Correlation of Chromosome Patterns in Leukemic Cells of Patients with Exposure to Chemicals and/or Radiation, 166

Clarkson University, Potsdam, NY

Hopke, P.K.

Radon: Atmospheric Chemistry of Radon Progeny in Laboratory and Real Indoor Atmospheres, 237

Cold Spring Harbor Laboratory, Cold Spring Harbor, NY

Henderson, M.

Human Genetics and Genome Analysis: A Practical Workshop for Public Policymakers and Opinion Leaders, 351

Marr, T.G.

A Computer System for Access to Distributed Genome Mapping Data, 352

Micklos, D.A.

Human Genetics and Genome Analysis: A Practical Workshop for Public Policymakers and Opinion Leaders, 351

Reiner, A.

A Computer System for Access to Distributed Genome Mapping Data, 352

Witkowski, J.

Human Genetics and Genome Analysis: A Practical Workshop for Public Policymakers and Opinion Leaders, 351

Collaborative Research, Inc., Waltham, MA

Moir, D.T.

Chimera-Free, High Copy Number Yeast Artificial Chromosome Libraries and Efficient Methods of Analysis, 353

Colorado, University of, Boulder, CO

Hanson, H.P.

Thermohaline Circulations and Global Climate Change, 799

Illangasekare, T.H.

Studies of Water Infiltration and Runoff in Subfreezing Snow on Regional Scales to Estimate Future Greenhouse-Induced Changes in Sea Level, 743

Meler, M.F.

Studies of Water Infiltration and Runoff in Subfreezing Snow on Regional Scales to Estimate Future Greenhouse-Induced Changes in Sea Level, 743

Walker, D.A.

Landscape Dynamics in the Arctic Foothills: Landscape Evolution and Vegetation Succession on Disturbances, 712

Colorado College, Colorado Springs, CO

McInerney, J.D.

Mapping & Sequencing the Human Genome: Science, Ethics, & Public Policy—Development & Distribution of Educational Materials for Use in High School Biology Classes, 354

Colorado Health Sciences Center, University of, Denver, CO

Hopkins, J.A.

cDNA Sequence-Tagged Site Map of the Human Genome: Methods Development and Applications Using Brain cDNAs, 355

Kao, F.-T.

Chromosome Region-Specific Libraries for Human Genome Analysis, 356

Khan, A.S.

cDNA Sequence-Tagged Site Map of the Human Genome: Methods Development and Applications Using Brain cDNAs, 355

Orpana, A.K.

cDNA Sequence-Tagged Site Map of the Human Genome: Methods Development and Applications Using Brain cDNAs, 355

Sikela, J.M.

cDNA Sequence-Tagged Site Map of the Human Genome: Methods Development and Applications Using Brain cDNAs, 355

Stevens, T.J.

cDNA Sequence-Tagged Site Map of the Human Genome: Methods Development and Applications Using Brain cDNAs, 355

Wilcox, A.S.

cDNA Sequence-Tagged Site Map of the Human Genome: Methods Development and Applications Using Brain cDNAs, 355

Yu, J.-W.

Chromosome Region-Specific Libraries for Human Genome Analysis, 356

Colorado State University, Fort Collins, CO

Borak, T.B.

Effects of Vegetation on Radon Transport Processes in Soil, 657

Coughenour, M.B.

Grassland/Atmospheric Response to Climate Change: Coupling Regional and Local Scales, 713

Cox, S.K.

Monitoring the Response of the Upper Troposphere/Lower Stratosphere to a Greenhouse Gas Scenario, 800

Jensen, T.

Parameterizations in High Resolution Isopycnal Wind-Driven Ocean Models, 744

Randall, D.A.

Development of an Advanced Finite-Difference Atmospheric General Circulation Model, 746

The Role of Clouds in Carbon Dioxide-Induced Climate Change, 745

The Use of Atmospheric Radiation Measurement Data to Test an Improved Parameterization of Upper Tropospheric Clouds for Use in Climate Models, 801

Parameterizations in High Resolution Isopycnal Wind-Driven Ocean Models, 744

Columbia University, New York, NY

Brown, S.

Chromosome Specific cDNAs and Sequence-Tagged Sites, 357

de Fatima Bonaldo, M.

Chromosome Specific cDNAs and Sequence Tagged Sites, 357

Druyan, L.M.

The Impact of Recent Model Improvements on Goddard Institute for Space Studies General Circulation Model Predictions of Climate Change, 747

Efstathiadis, A.

Chromosome Specific cDNAs and Sequence-Tagged Sites, 357

Hall, E.J.

Radiation Physics and Biology, 196

Jelenc, P.

Chromosome Specific cDNAs and Sequence-Tagged Sites, 357

Soares, M.B.

Chromosome Specific cDNAs and Sequence-Tagged Sites, 357

Zalder, M.

Radiation Physics and Biology, 196
Nanodosimetry and Nanodosimetric-Based Models of Radiation Action for Radon-Alpha Particles, 238

Columbia University, Palisades, NY**Broecker, W.S.**

Steady-State and Transient Modeling of Tracer and Nutrient Distributions in the Global Ocean, 858

The Effects of Changing Land Use on Carbon and Nitrogen in Mid-Latitude North American Soil and Rice Paddies, 836

Chipman, D.W.

Development of Gas Chromatographic System for Dissolved Organic Carbon Analysis in Seawater, 581

Karl, T.

Recent Changes of Weather Patterns in North America, 748

Kukla, G.

Recent Changes of Weather Patterns in North America, 748

Takahashi, T.CO₂ Measurements Along the World Ocean Circulation Experiment P-16 and 19 Sections in the South Pacific Ocean: A Joint Lamont-Doherty Geological Observatory/Woods Hole Oceanographic Institution Program, 859

Development of Gas Chromatographic System for Dissolved Organic Carbon Analysis in Seawater, 581

Measurements of Carbon Dioxide in the Southern Ocean Along the World Ocean Circulation Experiment S-4 Section, 860

Columbia University College of Physicians and Surgeons, New York, NY**Worgul, B.V.**

Low Dose Neutron: Late Effects: Cataractogenesis, 87

Columbia University Law School, New York, NY**Feltzians, I.**

Lawful Uses of Knowledge from the Human Genome Project, 358

Grad, F.

Lawful Uses of Knowledge from the Human Genome Project, 358

Holtzman, N.

Lawful Uses of Knowledge from the Human Genome Project, 358

Warburton, D.

Lawful Uses of Knowledge from the Human Genome Project, 358

Commonwealth Scientific and Industrial Research Organization, Mordialloc, VIC 3195 Australia**Platt, C.M.R.**

A Precise, Passive, Narrow-Beam Infrared Filter Radiometer and Its Use with Laser Radar in the Atmospheric Radiation Measurement Program, 359

Computational Biosciences, Inc., Ann Arbor, MI**Hartman, J.R.**

High Performance DNA and Protein Sequence Analysis on a Low Cost Parallel Processor Array, 360

Low Cost Massively Parallel Neurocomputing for Pattern Recognition in Macromolecular Sequences, 361

Comstock, Inc., Oak Ridge, TN**Talmage, J.E.**

Detection of Atmospheric Pollutants Using Infrared Lasers Produced by Stimulated Electron Raman Scattering, 564

Detection of Atmospheric Pollutants Using Infrared Lasers Produced by Stimulated Electron Raman Scattering, 239

Connecticut, University of, Storrs, CT**Berg, C.M.**

A Probe-Based Mapping Strategy for DNA Sequencing with Mobile Primers, 362

Strausbaugh, L.D.

A Probe-Based Mapping Strategy for DNA Sequencing with Mobile Primers, 362

Cornell University, Ithaca, NY**Ghiorse, W.C.**

Comparison of Distribution, Abundance, and Activities of Deep Subsurface Micro-Organisms at DOE Sites, 658

Masden, E.L.

Comparison of Distribution, Abundance, and Activities of Deep Subsurface Micro-Organisms at DOE Sites, 658

Morrison, G.H.

Subcellular Distribution of Boron for Boron Neutron Capture Therapy Using Ion Microscopy, 503

Defense Advanced Research Projects Agency, Arlington, VA**Entzminger, J.N.**

A JASON Study of Selected Topics for DOE, 802

Delaware, University of, Lewes, DE**Churchman, D.L.**

The Effect of Bacteria and Microbial Metabolites on Mineral Dissolution in Subsurface Environments, 659

Ullmann, W.J.

The Effect of Bacteria and Microbial Metabolites on Mineral Dissolution in Subsurface Environments, 659

Vandevivere, P.

The Effect of Bacteria and Microbial Metabolites
on Mineral Dissolution in Subsurface
Environments, 659

Welch, S.A.

The Effect of Bacteria and Microbial Metabolites
on Mineral Dissolution in Subsurface
Environments, 659

Denver, University of, Denver, CO**Murcray, D.G.**

Development of a Short-Wavelength Infrared Solar
Spectral Radiometer for the Atmospheric Radiation
Measurement Program, 803

Desert Research Institute, Reno, NV**Hudson, J.G.**

Linkage of Anthropogenic Aerosol to Clouds and
Climate, 804

Duke University, Durham, NC**Pirrung, M.C.**

Preparation of Oligonucleotide Arrays for Hybridization
Studies, 363

Reynolds, J.F.

Effects of Disturbances on Ecosystem Dynamics of
Tundra and Riparian Vegetation, 714
Modeling the Response of Plants and Ecosystems in
CO₂ and Climate Change, 837

Richards, J.F.

Spatial and Temporal Patterns of Biotic Exchanges
of CO₂ Between the Atmosphere and Tropical
Landscapes and their Role in the Global
Carbon Balance, 839

Strain, B.R.

Integration of Experimental and Modeling Approaches
in the Unmanaged Ecosystem Research Plan, 838

Duke University Medical Center, Durham, NC**Jaszczak, R.J.**

Single-Photon Emission Computed Tomography Assay
of Radiolabeled Monoclonal Antibodies, 504

Mercer, R.R.

Determination of the Cell Distribution and Mucous
Thickness in the Airways of the Lung for
Modeling Injury Caused by Inhaled Radon
and Radon Daughters, 88

Zalutsky, M.R.

Positron Emission Tomographic Imaging of Tumors
Using Monoclonal Antibodies, 505

Dynamics Technology, Inc., Torrance, CA**Chang, E.**

Development of a Moored Optical Instrument for
Measurement of Oceanic Particle Size and
Settling Rate, 582

East Anglia, University of, Norwich NR47TJ United Kingdom**Jones, P.D.**

Detection of CO₂-Induced Climate Change, 749

Wigley, T.M.L.

Detection of CO₂-Induced Climate Change, 749

Environmental Measurements Laboratory, New York, NY**Bogen, D.**

Analytical Development, 211
Natural Radioactivity in the Biosphere, 210

Helt, M.

Fallout Radionuclides in Deposition, Diet, and
Bone, 212

Pollutants in Surface and Tropospheric Air, 213

Pollutants in Deposition and the Biosphere, 546

Leifer, R.

Atmospheric Radiation Measurement Program
Support, 779

Lowder, W.

Environmental Radiation Research, 215
Radiation Transport and Dosimetry, 214
Radon, Thoron, and the Related Aerosols, 216

Eunice Kennedy Shriver Center for Mental Retardation, Waltham, MA**Natowicz, M.**

Studies of Genetic Discrimination, 364

Relly, P.

Genetic Data and Privacy: A Search for Model
Legislation, 365

Farachem Technology, Inc., Springfield, OH**Taylor, E.J.**

Field-Portable Instrumentation for Metal
Analysis, 240

Field-Portable Instrumentation for Metal
Analysis, 660

Fermi National Accelerator Laboratory, Batavia, IL**Walton, R.**

Fermilab National Environmental Research Park, 693

Florida State University, Tallahassee, FL**Balkwill, D.L.**

Establishment and Maintenance of a Subsurface
Microbial Culture Collection, 662

Phylogenetic Diversity Analysis of Deep
Subsurface Micro-Organisms, 661

Bauer, J.

Transformation Rates and Fate of Dissolved,
Colloidal, and Particulate Forms of Organic
Carbon in Ocean Margins, 583

Kasha, M.

Energy Transformation in Molecular Electronic Systems, 197

Lim, H.A.

Multiple Alignment and Homolog Sequence Database Compilation, 366

Reeves, R.H.

Phylogenetic Diversity Analysis of Deep Subsurface Micro-Organisms, 661

Rhodes, W.C.

Selective Excitation, Relaxation, and Energy Channeling in Molecular Systems, 198

Weatherly, G.L.

Numerical Studies of Bottom Boundary Layer Processes Along the Continental Margin, 584

Fred Hutchinson Cancer Research Center, Seattle, WA**Moolgavkar, S.H.**

Initiation-Promotion-Initiation Experiments with Radon and Cigarette Smoke: Lung Tumors in Rats, 89

Geotech Inc., Grand Junction, CO**Carroll, J.**

Extension of ^{210}Pb Geochronology with Inverse Numerical Techniques, 585

Golder Associates, Inc., Richland, WA**Russell, B.F.**

Drilling and Sampling Technology Research, 663

Harvard Medical School, Boston, MA**Church, G.M.**

Developing a Fully Integrated Technology for Sequencing Genomes as Large as Those of Humans, 368

Himawan, J.

Thioredoxin-Gene 5 Protein Interactions: Processivity of Bacteriophage T7 DNA Polymerase, 367

Richardson, C.C.

Thioredoxin-Gene 5 Protein Interactions: Processivity of Bacteriophage T7 DNA Polymerase, 367

Tabor, S.

Thioredoxin-Gene 5 Protein Interactions: Processivity of Bacteriophage T7 DNA Polymerase, 367

Harvard University, Cambridge, MA**Bazzaz, F.A.**

Integration of Experimental and Modeling Approaches to Study Competitive Interactions Among Plants Under Elevated CO_2 , 840

Hawaii, University of, at Manoa, Honolulu, HI**Thomas, D.M.**

Radon Transport in the Subsurface Environment: Natural Response and Structure-Induced Effects, 664

Hypres, Inc., Elmsford, NY**Radparvar, M.**

Imaging Systems for Biomedical Applications, 506

Idaho National Engineering Laboratory, Idaho Falls, ID**Andrews, G.F.**

Complete Degradation of Mixed Halocarbons by Methanogenic and Methanotrophic Microbial Communities, 620

Bishop, C.W.

Hydrogeologic and Geochemical Controls on Micro-Organisms in Subsurface Formations, 619

Bruns, D.

Planning Guide to Long-Term Ecological Monitoring for Global Change at DOE Research Parks, 694

Colwell, F.S.

Complete Degradation of Mixed Halocarbons by Methanogenic and Methanotrophic Microbial Communities, 620

Deep Subsurface Sample Analysis at Idaho National Engineering Laboratory, 621

Drilling and Sampling Technology Research, 663

Delmore, J.E.

Neutral Beam Microprobe, 217

Markham, O.D.

INEL National Environmental Research Park, 695
INEL Radioecology and Ecology Program, 622

Stormberg, G.J.

Deep Subsurface Sample Analysis at Idaho National Engineering Laboratory, 621

Wiersema, R.J.

Boron Neutron Capture Therapy Research Program, 460

Illinois, University of, Urbana, IL**Brown, S.**

Spatial and Temporal Patterns of Biotic Exchanges of CO_2 Between the Atmosphere and Tropical Landscapes and Their Role in the Global Carbon Balance, 841

Katzenellenbogen, J.A.

Fluorine-18-Labeled Androgens and Progestins: Imaging Agents for Tumors of Prostate and Breast, 507

Rittmann, B.E.

Fundamental Quantitative Analysis of Microbial Activity in Aquifer Bioreclamation, 665

Schlesinger, M.E.

Greenhouse Gas-Induced Climate Change, 750

Valocchi, A.J.

Fundamental Quantitative Analysis of Microbial Activity in Aquifer Bioreclamation, 665

Illinois State Water Survey, Champaign, IL**Williams, A.L.**

Determining the Chemical Composition of Cloud Condensation Nuclei, 805

Indiana University, Bloomington, IN**Hites, R.A.**

Toxic Organic Compounds from Energy Production, 241

Inhalation Toxicology Research Institute, Albuquerque, NM**Bechtold, W.E.**

Influence of Modifying Factors on Metabolic Fate of Inhaled Organic Compounds, 17

Belinsky, S.A.

Mechanisms of Chemically Induced Carcinogenicity, 18

Bice, D.E.

Role of Immune Responses in Respiratory Diseases, 19

Boecker, B.B.

Toxicity of Injected Actinides, 20

Cheng, Y.S.

Dynamics of Radon Daughter Interactions with Indoor Aerosols, 218

Dahl, A.R.

Influence of Respiratory Tract Metabolism on Effective Dose, 21

Finch, G.L.

Mechanisms of Granulomatous Disease from Inhaled Beryllium, 22

Guilmette, R.A.

Effective Dose from Inhaled Nuclear Energy Materials, 23

Hahn, F.F.

Links Between Radiation-Induced Lung Cancer in Laboratory Animals and Humans, 24

Harkema, J.R.

Morphology of the Respiratory Tract and Response to Injury, 25

Henderson, R.F.

Cellular and Biochemical Mediators of Respiratory Tract Diseases, 26

Johnson, N.R.

Radiation Dose and Injury to Critical Lung Cells from Radon, 27

Jones, R.K.

Protection of Human Subjects, 28

Kelly, G.

Molecular Mechanisms of Radiation-Induced Cancer, 29

Lechner, J.F.

Lung Cancer in Uranium Miners—Gene Dysfunctions, 32

Mechanism of Radiation-Induced Cancer, 31

Premalignant Events in Radiation-Induced Lung Cancer, 30

Muggenburg, B.A.

Dose-Response Relationships for Inhaled Radionuclides, 33

Yeh, H.-C.

Biologically Relevant Properties of Energy-Related Aerosols, 34

Deposition of Radon and Radon Progeny in the Respiratory Tract, 35

Institute for Genomic Research, The, Gaithersburg, MD**Adams, M.**

Expressed Sequence Tags from Human Brain cDNAs for Genome Mapping, 370

Dubnick, M.

Expressed Sequence Tags from Human Brain cDNAs for Genome Mapping, 370

Fields, C.A.

Expressed Sequence Tags from Human Brain cDNAs for Genome Mapping, 370

Identification of Genes in Anonymous DNA Sequences, 369

Kelley, J.

Expressed Sequence Tags from Human Brain cDNAs for Genome Mapping, 370

Kerlavage, A.

Expressed Sequence Tags from Human Brain cDNAs for Genome Mapping, 370

Moreno, R.

Expressed Sequence Tags from Human Brain cDNAs for Genome Mapping, 370

Nagle, J.

Expressed Sequence Tags from Human Brain cDNAs for Genome Mapping, 370

Soderlund, C.A.

Identification of Genes in Anonymous DNA Sequences, 369

Venter, J.C.

Expressed Sequence Tags from Human Brain cDNAs for Genome Mapping, 370

Intelligenetics Inc, Mountain View, CA**Kristofferson, D.**

The BIOSCI Electronic Newsgroup Network for the Biological Sciences, 371

Leon, E.

The BIOSCI Electronic Newsgroup Network for the Biological Sciences, 371

Iowa State University, Ames, IA**Gutowski, W.J.**

Modeling of Land-Surface/Atmospheric Dynamics for CHAMMP, 751

Johns Hopkins University, The, Baltimore, MD**Grossman, L.**

Role of DNA Damage and Repair in Chronic Disease, 167

Stone, A.T.

Release of Oxide-Bound Toxic Metals by Naturally Occurring and Contaminant-Derived Organic Compounds: The Role of Complexant, Reductant, and Adsorptive Characteristics, 666

Johns Hopkins University School of Hygiene and Public Health, The, Baltimore, MD**Lesko, S.A.**

Genes and Gene Expression: Localization, Damage, and Control—A Multilevel and Interdisciplinary Study, 168

Miller, P.S.

Genes and Gene Expression: Localization, Damage, and Control—A Multilevel and Interdisciplinary Study, 168

Swift, D.L.

Regional Aerosol Deposition in Human Upper Airways, 90

Ts'o, P.

Genes and Gene Expression: Localization, Damage, and Control—A Multilevel and Interdisciplinary Study, 168

Johns Hopkins University School of Medicine, The, Baltimore, MD**Dannals, R.F.**

Synthesis of Tracers Using Automated Radiochemistry and Robotics, 508

Francomano, C.

A Human Genome Database, 372

Matheson, N.W.

A Human Genome Database, 372

McKusick, V.A.

A Human Genome Database, 372

Pearson, P.L.

A Human Genome Database, 372

Robbins, R.J.

A Human Genome Database, 372

K.C. Research Corporation, Littleton, CO**Cerni, T.A.**

A Marine Boundary Layer Water Vapor Flux Sensor, 586

Kansas Medical Center, University of, Kansas City, KS**Collins, D.L.**

Human Genetics Education for Middle and Secondary Science Teachers, 373

Schimke, R.N.

Human Genetics Education for Middle and Secondary Science Teachers, 373

Segebrecht, L.

Human Genetics Education for Middle and Secondary Science Teachers, 373

Kansas State University, Manhattan, KS**Owensby, C.E.**Rangeland-Plant Response to Elevated CO₂, 842**Large Scale Biology Corporation, Rockville, MD****Anderson, N.G.**

Instrumentation for Automated Colony Processing, 374

Lawrence Berkeley Laboratory, Berkeley, CA**Alpen, E.L.**

Long Term Biological Effects: Carcinogenic Effects of High Linear Energy Transfer Radiation, 37

Angel, S.M.

An Investigation of Chemical Flow Characteristics Using Fiber Optic Sensor Technology, 627

Attwood, D.T.

Biological X-Ray Microscopy Resource Center, 432

Benner, W.H.

Advanced Detectors for Mass Spectroscopy, 277

Benson, S.M.

An Interdisciplinary Approach to Spatial Characterization of Contaminant Transport, 624

Bissell, M.J.

Molecular Carcinogenesis: Molecular Mechanisms Underlying Tissue-Specific Gene Expression, 122

Blakely, E.A.

Clinical Heavy Ion Radiobiology, 461

Molecular Mechanism of Cell Effect: Molecular and Cellular Effects of Ionizing Radiations, 38

Brennan, T.M.

Sequencing by Hybridization, 273

Budinger, T.F.

Development of Radionuclides for Medical Imaging Purposes, 464
Human Brain and Heart Metabolism and Flow Measurements by Noninvasive Techniques, 465

Castro, J.R.

Clinical Heavy Ion Radiobiology, 461

Chatterjee, A.

Diagnostic Use of High Energy Radioactive Beams in Cancer Therapy and Nuclear Medicine, 462
Radiological Physics and Chemistry: Mechanistic Theoretical Models for Radiation-Induced Mutation and Transformation, 180

Cheng, J.

Human Genome Center/Isolation of Chromosome 21 cDNA Clones, 267
Human Genome Center/Rapid Isolation and Organization of Chromosome 21 YAC Clones, 269
Human Genome Center/Rapid Isolation and Organization of Chromosome 21 YAC Clones, 268

Cramer, S.P.

Biological X-Ray Spectroscopy Resource Center, 431

Daisey, J.M.

Air Pollutant Exposures in Buildings, 36

Derenzo, S.E.

Improved Instrumentation for Positron Tomography, 466

Ebbe, S.N.

Vascular and Blood Diseases, 467

Esposito, M.S.

Mitotic Recombination and DNA Repair, 123

Fabrikant, J.I.

Effects of Heavy Particle Radiation, 468
Heavy Ion Radiosurgery, 469

Fisk, W.J.

Experimental and Theoretical Investigations of Radon Availability, Migration, and Entry, 623

Gadgil, A.J.

Characterization of Airborne Radon Concentrations, 219

Gingrich, J.C.

Human Genome Center/Chromosome 21 Physical Mapping, 270

Gold, L.S.

Risk Assessment in Carcinogenesis, 39

Gusfield, D.

Human Genome Center/Algorithms for Mapping and Sequencing the Human Genome, 281

Hearst, J.

Self-Processing Ribonucleic Acid, 425

Huesman, R.H.

Human Brain and Heart Metabolism and Flow Measurements by Noninvasive Techniques, 465

Hunkapiller, T.

Laboratory Information Management System for Megabase Sequencing, 279

Jaklevic, J.M.

Advanced Detectors for Mass Spectroscopy, 277
Human Genome Center/Atomic Force Microscopy/Scanning Tunneling Microscopy, 274
Human Genome Center/Automation and Robotics in Support of the Human Genome Center, 275
Human Genome Center/Fluorescent Detection of Biological Probes, 276
Semiconductor Radiation Detector Technology, 220
Semiconductor X-Ray Detectors for Synchrotrons, 221

Katz, J.

Advanced Detectors for Mass Spectroscopy, 277

Kim, S.-H.

Catalytic Antibodies, 429
Multiuser Crystallography Facility, 427
Structural Biophysics, 426

Klein, M.

Biophysical Chemistry, 428

Kulp, T.J.

An Investigation of Chemical Flow Characteristics Using Fiber Optic Sensor Technology, 627

LLacer, J.

Application of Statistically Based Algorithms to Emission Tomography, 463

Lawler, E.

Human Genome Center/Algorithms for Mapping and Sequencing the Human Genome, 281

Lewis, S.

Laboratory Information Management System for Megabase Sequencing, 279

Liburdy, R.P.

Biological Effects of Magnetic Fields, 40

Long, J.C.S.

An Interdisciplinary Approach to Spatial Characterization of Contaminant Transport, 624

Majer, E.L.

An Interdisciplinary Approach to Spatial Characterization of Contaminant Transport, 624

Markowitz, V.M.

Human Genome Center/Database Tools for Scientific Applications, 278
Laboratory Information Management System for Megabase Sequencing, 279

Martin, C.

Human Genome Center/100 Megabase Physical Mapping, 272

Human Genome Center/Large Scale DNA Sequencing, 271

McCarthy, J.L.

Human Genome Center/Information Management System, 280

Mortimer, R.K.

Genetic Study on Yeast, 124

Narasimhan, T.N.

Experimental and Theoretical Investigations of Radon Availability, Migration, and Entry, 623

Narla, M.

Bone Marrow Stem Cells and Stromal Microenvironment, 41

Nero, A.

Air Pollutant Exposures in Buildings, 36

Nitsche, H.

Experimental Investigation of Thermodynamic Properties of Chemical Species Present in Mixed Organic-Radionuclide Wastes, 625

Novakov, T.

Aerosol and Cloud Chemistry, 547

Modification of Cloud Optical Properties by Aerosols, 780

Olken, F.

Human Genome Center/Algorithms for Mapping and Sequencing the Human Genome, 281

Ostrander, E.

Human Genome Center/High Resolution Genetic Mapping, 283

Palazzolo, M.

Human Genome Center/100 Megabase Physical Mapping, 272

Human Genome Center/Large Scale DNA Sequencing, 271

Perry, D.L.

The Chemistry of Toxic Organic/Metal Ion (Radionuclide) Co-Contaminants Involved in Subsurface Transport, 626

Rine, J.D.

Human Genome Center, 265

Rossington, C.S.

Semiconductor X-Ray Detectors for Synchrotrons, 221

Rothman, S.S.

Application of X-Ray Microscopy To Study Protein Secretion, 424

Scherer, S.

Human Genome Center/Distribution of DNA Sequences as Signals of Origin, 284

Schultz, P.

Catalytic Antibodies, 429

Center for Biomolecular Design, 125

Sextro, R.G.

Characterization of Airborne Radon Concentrations, 219

Experimental and Theoretical Investigations of Radon Availability, Migration, and Entry, 623

Spengler, S.

Human Genome Center/Coordinating Committee Administration, 266

Stampfer, M.R.

Rapid Transformation Assay: Induction and Detection of In Vitro Transformation of Human Mammary Epithelial Cells, 42

Tinoco, Jr., I.

Self-Processing Ribonucleic Acid, 425

Wemmer, D.

Biomolecular Structure Analysis by Nuclear Magnetic Resonance, 430

Catalytic Antibodies, 429

Self-Processing Ribonucleic Acid, 425

Wollenberg, H.A.

Experimental and Theoretical Investigations of Radon Availability, Migration, and Entry, 623

Zorn, M.D.

Human Genome Center/Software and Data Resource Facility, 282

Lawrence Livermore National Laboratory, Livermore, CA**Angel, S.M.**

Remote Detection of Environmental Contaminants Using Fiber Optic Spectroscopy, 222

Balhorn, R.L.

Chromatin Structure in Mammalian Sperm, 126

DNA/Scanning Tunneling Microscopy, 433

X-Ray Holography, 434

Bigbee, W.L.

Molecular Mechanisms of Mutagenesis: An In Vitro Glycophorin A-Based Cellular Model, 127

Brandriff, B.F.

DNA Sequence Mapping by Fluorescence In Situ Hybridization, 293

Human Sperm Chromatin and Chromosomes, 43

Branscomb, E.W.

Computational Support for the Human Genome Center: Statistical and Mathematical Analysis, Data Processing, and Databasing, 286

Carrano, A.V.

Assembly, Closure, and Characterization of a Chromosome 19 Contig Map, 292
 Coding Region Isolation, Mapping, and Characterization, 290
 Core Facility, 287
 Human Genome Center, 285
 Interdigitation of the Physical and Generic Maps of Human Chromosome 19, 291

Dannevik, W.P.

Climate Systems Modeling on Massively Parallel Computers I: Global Ocean Circulation Model, 722

de Jong, P.J.

Assembly, Closure, and Characterization of a Chromosome 19 Contig Map, 292
 National Laboratory Gene Library Project, 289
 New Mapping Strategies, 288

Garcia, E.

Assembly, Closure, and Characterization of a Chromosome 19 Contig Map, 292
 Core Facility, 287

Gates, W.L.

Climate Model Diagnosis and Intercomparison, 723
 Cray Computer, 724

Gudiksen, P.H.

Complex Terrain Studies, 548

Jones, I.M.

Mechanisms of Somatic Mutation in Mammalian Cells, 44

Knapp, R.B.

Application of Particle Methods to Multicomponent Geochemical Reactive Transport Problems, 628

Kulp, T.J.

Spectroscopic Study of H₂O Absorption in the 8- to 14-Micrometer Atmospheric Window: Measurement of New Line and Continuum Parameters and Investigation of Far-Wing Phenomena, 781

Langlois, R.G.

Human Mutagenesis: Methods, Applications, Animal Models, and Mechanisms, 128

Lennon, G.

Coding Region Isolation, Mapping, and Characterization, 290
 Interdigitation of the Physical and Generic Maps of Human Chromosome 19, 291

Leone, Jr., J.M.

Mesoscale Emergency Response, 549

Lucas, J.N.

Flow and Analytical Cytogenetics, 131

MacCracken, M.C.

Carbon Dioxide Effects Research, 725

Computer Hardware Advanced, Mathematics, and Model Physics Initiative Organization, 726

Mohrenweiser, H.W.

Assembly, Closure, and Characterization of a Chromosome 19 Contig Map, 292
 Coding Region Isolation, Mapping, and Characterization, 290
 Core Facility, 287
 Human Germinal Gene Mutation Project, 129
 Interdigitation of the Physical and Generic Maps of Human Chromosome 19, 291

Nelson, D.

Computational Support for the Human Genome Center: Statistical and Mathematical Analysis, Data Processing, and Databasing, 286

Olsen, A.

Assembly, Closure, and Characterization of a Chromosome 19 Contig Map, 292
 Core Facility, 287

Penner, J.E.

Modeling in Support of DOE's Participation in the North Atlantic Regional Experiment, 550
 The Role of Aerosols and Cloud Microphysics in Climate and Climate Change, 782

Perry, M.

Carbon Dioxide Effects Research, 725

Slezak, T.

Computational Support for the Human Genome Center: Statistical and Mathematical Analysis, Data Processing, and Databasing, 286

Taylor, K.E.

Carbon Dioxide Effects Research, 725

Thompson, L.H.

Molecular Genetics of DNA Repair, 130

Tompson, A.F.B.

Application of Particle Methods to Multicomponent Geochemical Reactive Transport Problems, 628

Trask, B.J.

DNA Sequence Mapping by Fluorescence In Situ Hybridization, 293
 Flow and Analytical Cytogenetics, 131
 National Laboratory Gene Library Project, 289

Trebes, J.E.

X-Ray Holography, 434

Tucker, J.D.

Molecular Cytogenetics, 45

van den Engh, G.J.

Instrumentation for Cytogenetics and Gene Mapping, 294
 National Laboratory Gene Library Project, 289
 Flow and Analytical Cytogenetics, 131

Wuebbles, D.J.

Scientific Development of the Advanced Parallel Chemistry Climate Model, 728
Trace Gas Interactions in the Global Atmosphere, 727

Wyrobek, A.J.

Detection of Gene Mutations and Chromosomal Abnormalities in Human Sperm, 132

Library of Congress, The, Washington, DC
Murphy, D.C.

Pilot Resident Fellow Program in Science and Technology: Bioethics Issues in Molecular Genetics, 375

Linus Pauling Institute of Science and Medicine, Palo Alto, CA
Jurka, J.

Efficient Identification and Analysis of Low and Medium Frequency Repeats, 376

Los Alamos National Laboratory, Los Alamos, NM
Anzick, S.L.

High Precision Mapping of Yeast Artificial Chromosome Clones onto Chromosome 21 by Fluorescence In Situ Hybridization and Image Analysis, 304

Baker, R.J.

Chromosomal Organization of Human Repetitive DNA Sequences, 307

Balding, D.

Pooling Yeast Artificial Chromosome Libraries for Screening with Unique Sequences, 296

Barnes, F.

Remote Sensing of Surface Fluxes Important to Cloud Development, 783
Los Alamos National Environmental Research Park, 696

Baumgardner, J.R.

Comparison of Methods for Solving the Spherical Shallow Water Equations on the Connection Machine, 732

Beugelsdijk, T.J.

Automated Methods for Large Scale Physical Mapping, 312

Bossert, J.

Terrain-Influenced Meteorology, 551

Bradbury, E.M.

Control of Cell Cycle and Transformation, 133

Bruce, D.

Pooling Yeast Artificial Chromosome Libraries for Screening with Unique Sequences, 296

Bruno, W.

Pooling Yeast Artificial Chromosome Libraries for Screening with Unique Sequences, 296

Burks, C.

Construction of Restriction Maps Using Simulated and Real Data, 310

Callen, D.F.

Construction of a 1.6 Megabase Average Resolution Sequence-Tagged Site Map of Human Chromosome 16, 297
Construction of a Cosmid, Yeast Artificial Chromosome, and Sequence-Tagged Site Physical Map of Human Chromosome 16, 299

Campbell, E.W.

Construction and Characterization of Human Genomic Yeast Artificial Chromosome Library with a Low Frequency of Chimeric Clones, 308
High Precision Mapping of Yeast Artificial Chromosome Clones onto Chromosome 21 by Fluorescence In Situ Hybridization and Image Analysis, 304

Chen, D.J.

Molecular Genetics of Radiation Repair Genes, 134
Molecular Mechanisms of Radiation-Induced Mutations, 46
Regulate Mammalian Cell Cycle Progression, 48

Cinkosky, M.

Construction of a Cosmid, Yeast Artificial Chromosome, and Sequence-Tagged Site Physical Map of Human Chromosome 16, 299

Clements, W.E.

Remote Sensing of Surface Fluxes Important to Cloud Development, 783
Terrain-Influenced Meteorology, 551

Cole, D.A.

Detection and Treatment of Lung Cancer Using ⁶⁷CuTCPP, 471

Imaging Agents for Lymph Nodes and Inflammatory Lesions, 470

Cooper, D.I.

Application of a Solar-Blind LIDAR for Atmospheric and Ecological Studies, 698

D'Anna, J.A.

Regulate Mammalian Cell Cycle Progression, 48

Deaven, L.L.

Chromosome Structure and Function, 135
Construction and Characterization of Human Genomic Yeast Artificial Chromosome Library with a Low Frequency of Chimeric Clones, 308
Construction of a Cosmid, Yeast Artificial Chromosome, and Sequence-Tagged Site Physical Map of Human Chromosome 16, 299
High Precision Mapping of Yeast Artificial Chromosome Clones onto Chromosome 21 by

- Fluorescence In Situ Hybridization and Image Analysis, 304
Human Recombinant DNA Library, 298
Systematic Generation of Chromosome 5 Specific Sequence-Tagged Sites, 301
- Denison, K.S.**
Sequencing and Mapping of cDNAs from a Paternally Encoded Human Pregnancy, 300
- Doggett, N.A.**
Construction of a Cosmid, Yeast Artificial Chromosome, and Sequence-Tagged Site Physical Map of Human Chromosome 16, 299
Construction of Restriction Maps Using Simulated and Real Data, 310
Pooling Yeast Artificial Chromosome Libraries for Screening with Unique Sequences, 296
- Eichinger, W.E.**
Application of a Solar-Blind LIDAR for Atmospheric and Ecological Studies, 698
- Eller, P.G.**
Co-Contaminant Reaction Chemistry at Interfaces, 629
- Flicker, J.W.**
Construction of a Cosmid, Yeast Artificial Chromosome, and Sequence-Tagged Site Physical Map of Human Chromosome 16, 299
- Flynn, E.R.**
Imaging Function in the Human Brain, 474
- Ford, A.**
Pooling Yeast Artificial Chromosome Libraries for Screening with Unique Sequences, 296
- Gatewood, J.M.**
A Loosely Coupled, Distributed Laboratory Notebook for the cDNA Community, 309
Sequencing and Mapping of cDNAs from a Paternally Encoded Human Pregnancy, 300
- Goodwin, E.H.**
Chromosome Damage in the 1 Rad Region, 47
Strand-Specific Orientation of Satellite DNA Sequences Determined by Fluorescence In Situ Hybridization, 305
- Grady, D.L.**
Human Recombinant DNA Library, 298
Systematic Generation of Chromosome 5 Specific Sequence-Tagged Sites, 301
- Gurley, L.R.**
Molecular Biology of Cell Cycle Dependent Genomic Structure, 136
Regulate Mammalian Cell Cycle Progression, 48
- Hildebrand, C.E.**
Construction of a Cosmid, Yeast Artificial Chromosome, and Sequence-Tagged Site Physical Map of Human Chromosome 16, 299
- Construction of Restriction Maps Using Simulated and Real Data, 310
- Jackson, P.J.**
Plant Physiology, 697
- Jett, J.H.**
Rapid DNA Sequencing Based on Fluorescence Detection of Single Molecules, 302
- Kao, C.Y.J.**
Cloud Parameterization in Climate Models, 786
Interfacing Between a Hierarchy of Numerical Models in the Atmospheric Radiation Measurement Program, 785
- Keller, R.A.**
Rapid DNA Sequencing Based on Fluorescence Detection of Single Molecules, 302
- Kraemer, P.M.**
Karyotype Instability and Neoplasia Studies, 137
- Lee, J.T.**
Terrain-Influenced Meteorology, 551
- Lehnert, B.E.**
Pulmonary Damage, 138
- Lemanski, C.L.**
Sequencing and Mapping of cDNAs from a Paternally Encoded Human Pregnancy, 300
- Lobb, R.**
Sequencing and Mapping of cDNAs from a Paternally Encoded Human Pregnancy, 300
- Longmire, J.L.**
Human Recombinant DNA Library, 298
- MacInnes, M.A.**
Transgenic Cell Models of Human Radiation Sensitivity, 49
- Macken, C.**
Pooling Yeast Artificial Chromosome Libraries for Screening with Unique Sequences, 296
- Malone, R.C.**
Computer Hardware, Advanced Mathematics, and Model Physics, 729
- Margolin, L.G.**
Predictability in Numerical Modeling of Ocean Dynamics, 731
- Marrone, B.L.**
High Precision Mapping of Yeast Artificial Chromosome Clones onto Chromosome 21 by Fluorescence In Situ Hybridization and Image Analysis, 304
- Martin, J.C.**
Rapid DNA Sequencing Based on Fluorescence Detection of Single Molecules, 302

- McCormick, M.K.**
Construction and Characterization of Human Genomic Yeast Artificial Chromosome Library with a Low Frequency of Chimeric Clones, 308
Construction of a Cosmid, Yeast Artificial Chromosome, and Sequence-Tagged Site Physical Map of Human Chromosome 16, 299
High Precision Mapping of Yeast Artificial Chromosome Clones onto Chromosome 21 by Fluorescence In Situ Hybridization and Image Analysis, 304
Human Recombinant DNA Library, 298
Pooling Yeast Artificial Chromosome Libraries for Screening with Unique Sequences, 296
- McPherson, J.D.**
Systematic Generation of Chromosome 5 Specific Sequence-Tagged Sites, 301
- Medvick, P.A.**
Automated Methods for Large Scale Physical Mapping, 312
- Meyne, J.**
Genome Organization and Function, 306
Strand-Specific Orientation of Satellite DNA Sequences Determined by Fluorescence In Situ Hybridization, 305
- Morris, D.E.**
Co-Contaminant Reaction Chemistry at Interfaces, 629
- Moyzis, R.K.**
Center for Human Genome Studies, 295
Construction and Characterization of Human Genomic Yeast Artificial Chromosome Library with a Low Frequency of Chimeric Clones, 308
Construction of a Cosmid, Yeast Artificial Chromosome, and Sequence-Tagged Site Physical Map of Human Chromosome 16, 299
Genetic Analysis of Yeast Artificial Chromosome Following Yeast Transformation and Mitotic Growth, 303
Genome Organization and Function, 306
Human Recombinant DNA Library, 298
Systematic Generation of Chromosome 5 Specific Sequence-Tagged Sites, 301
- Munk, C.**
Construction and Characterization of Human Genomic Yeast Artificial Chromosome Library with a Low Frequency of Chimeric Clones, 308
- Ott, K.C.**
Complementary Positron Emission Tomography and Therapeutic Radiopharmaceuticals, 472
- Pecherer, R.M.**
A Loosely Coupled, Distributed Laboratory Notebook for the cDNA Community, 309
- Peterson, E.J.**
Complementary Positron Emission Tomography and Therapeutic Radiopharmaceuticals, 472
Medical Radioisotope Research Program, 473
- Porch, W.M.**
Ocean Cloud/Climate Linkage Study, 784
Remote Sensing of Surface Fluxes Important to Cloud Development, 783
- Raju, M.R.**
Dosimetry and Cell Killing, 50
Radiobiology of Ultrasoft X Rays, 181
- Ratliff, R.L.**
Genome Organization and Function, 306
- Resnick, M.**
Genetic Analysis of Yeast Artificial Chromosome Following Yeast Transformation and Mitotic Growth, 303
- Robinson, D.L.**
Systematic Generation of Chromosome 5 Specific Sequence-Tagged Sites, 301
- Saunders, E.**
Construction and Characterization of Human Genomic Yeast Artificial Chromosome Library with a Low Frequency of Chimeric Clones, 308
- Schor, P.**
Construction and Characterization of Human Genomic Yeast Artificial Chromosome Library with a Low Frequency of Chimeric Clones, 308
- Shera, E.B.**
Rapid DNA Sequencing Based on Fluorescence Detection of Single Molecules, 302
- Shera, K.**
Construction and Characterization of Human Genomic Yeast Artificial Chromosome Library with a Low Frequency of Chimeric Clones, 308
- Smith, R.D.**
Massively Parallel Global Ocean Modeling, 733
- Soderlund, C.**
Construction of Restriction Maps Using Simulated and Real Data, 310
- Stallings, R.L.**
Construction of a 1.6 Megabase Average Resolution Sequence-Tagged Site Map of Human Chromosome 16, 297
Construction of a Cosmid, Yeast Artificial Chromosome, and Sequence-Tagged Site Physical Map of Human Chromosome 16, 299
- Strniste, G.F.**
Mechanisms of Radiation and Chemical Genetic Toxicology, 139

Sutherland, G.R.

Construction of a Cosmid, Yeast Artificial Chromosome, and Sequence-Tagged Site Physical Map of Human Chromosome 16, 299

Tlee, J.J.

Application of a Solar-Blind LIDAR for Atmospheric and Ecological Studies, 698

Torney, D.C.

Construction of a Cosmid, Yeast Artificial Chromosome, and Sequence-Tagged Site Physical Map of Human Chromosome 16, 299
Pooling Yeast Artificial Chromosome Libraries for Screening with Unique Sequences, 296

Trewhella, J.

Biological Neutron Scattering, 435

Wagner, R.P.

Systematic Generation of Chromosome 5 Specific Sequence-Tagged Sites, 301

Wasmuth, J.J.

Systematic Generation of Chromosome 5 Specific Sequence-Tagged Sites, 301

Wharton, W.

Regulation of Mammalian Cell Proliferation, 140

White, A.B.

Computer Hardware, Advanced Mathematics, and Model Physics CM-5 Support, 730

Whittaker, C.

Pooling Yeast Artificial Chromosome Libraries for Screening with Unique Sequences, 296

Wood, C.C.

Imaging Function in the Human Brain, 474

Yesley, M.S.

Ethical, Legal, and Social Issues Projects, 311

Yoshida, T.M.

High Precision Mapping of Yeast Artificial Chromosome Clones onto Chromosome 21 by Fluorescence In Situ Hybridization and Image Analysis, 304

Zweig, G.

Modeling of Cochlear Mechanisms, 475

Louisiana State University, Baton Rouge, LA**Kumar, D.**

A Physicochemical Study of Some Areas of Fundamental Significance to Biophysics, 199

Lee, W.R.

Mutagenic Effects of Tritium on DNA of *Drosophila melanogaster*, 169

McGlynn, S.P.

A Physicochemical Study of Some Areas of Fundamental Significance to Biophysics, 199

Louisiana Universities Marine Consortium, Chauvin, LA**Dagg, M.**

Assimilation and Transfer of Carbon in Oligotrophic and Eutrophic Coastal Water Columns, 587

Maine, University of, Walpole, ME**Mayer, L.M.**

Adsorption Control of Organic Carbon Burial in Ocean Margin Sediments, 588

Marine Biological Laboratory, Woods Hole, MA**Fry, B.**

Origins and Fates of Dissolved Organic Matter Along the New England Continental Margin, 589

Maryland, University of, College Park, MD**Baer, F.**

Exploitation of Parallelism in Climate Models, 752

Ellingson, R.G.

Intercomparison of Radiation Codes in Climate Models Phase II: Verification and Calibration, 806

Kinter, J.L.

Variability and Predictability of the Coupled Ocean-Atmosphere-Land Climate System, 753

Robock, A.

Volcanic Signal in Global Change, 754

Massachusetts, University of, Amherst, MA**Bradley, R.S.**

Climate System Research: Studies of Global and Regional Instrument Data, 755

Massachusetts General Hospital, Boston, MA**Brownell, G.L.**

High Resolution Tomographic Instrument Development, 509

Parrish, J.A.

Center of Excellence in Laser Medicine, 510

Massachusetts Institute of Technology, Boston, MA**Yanch, J.C.**

Accelerator-Based Epithermal Neutron Capture Therapy: Design of Neutron Source and Irradiation Facility, 511

Massachusetts Institute of Technology, Cambridge, MA**Adelstein, J.S.**

Short-Lived Radiopharmaceuticals, 512

Emanuel, K.A.

Development of an Advanced Representation of Cumulus Convection, 756

Gabra, N.

Robust Detailed Mapping of the Human Genome, 377

Gachwend, P.P.

Colloids in Groundwater: Their Mobilization, Subsurface Transport, and Sorption Affinity for Toxic Chemicals, 667

Hecht, N.B.

Robust Detailed Mapping of the Human Genome, 377

Lerman, L.S.

Robust Detailed Mapping of the Human Genome, 377

Schmitt, E.

Robust Detailed Mapping of the Human Genome, 377

Thilly, W.G.

Mutagenesis of Human Cells In Vivo and In Vitro, 170

Miami, University of, Miami, FL

Zika, R.G.

Use of a Laser-Based Monitoring Technique to Measure Trace Gas Fluxes Across the Air-Sea Interface, 807

Michigan, University of, Ann Arbor, MI

Boothman, B.A.

Role of X-Ray-Induced Transcripts in Adaptive Survival Responses Following X Rays, 92

Hayes, K.F.

The Influence of Interfacial Properties on Two-Phase Liquid Flow of Organic Contaminants in Groundwater, 668

Kopelman, R.

Nanometer Scale Exciton Spectroscopy and Photochemistry: Dynamic Imaging of DNA Structure-Activity Relations and Radiation Signatures, 242

Scanning Molecular Exciton Microscopy: A New Approach to Gene Sequencing, 378

Langmore, J.

Scanning Molecular Exciton Microscopy: A New Approach to Gene Sequencing, 378

Makarov, V.

Scanning Molecular Exciton Microscopy: A New Approach to Gene Sequencing, 378

Neel, J.V.

Studies of Human Mutation Rates, 91

Orr, B.

Scanning Molecular Exciton Microscopy: A New Approach to Gene Sequencing, 378

Michigan Medical Center, University of, Ann Arbor, MI

Kuhl, D.E.

New Techniques for Positron Emission Tomography in the Study of Human Neurological Disorders, 513

Radiopharmaceuticals for Diagnosis and Treatment, 514

Schwaiger, M.

Noninvasive Evaluation of the Cardiac Autonomic Nervous System by Positron Emission Tomography, 515

Michigan State University, East Lansing, MI

Boyd, S.A.

Physicochemical and Microbiological Factors Influencing the Bioavailability of Organic Contaminants in Subsoils, 669

Michigan State University College of Osteopathic Medicine, East Lansing, MI

McCormick, J.J.

Malignant Transformation of Diploid Human Fibroblasts by Transfection of Oncogenes, 171

Minnesota, University of, Minneapolis, MN

McMurry, P.H.

Ultrafine Aerosol Size Distributions and Sulfuric Acid Vapor Pressures: Implications for New Particle Formation in the Atmosphere, 565

Missouri, University of, Columbia, MO

Schlemper, E.O.

Bifunctional Chelates of Rh¹⁰⁵ and Au¹⁹⁹ as Potential Radiotherapeutic Agents, 516

Volkert, W.A.

Production of Radiolabeled Monoclonal Antibody Conjugates by Photoaffinity Labeling, 517

Molecular Dynamics, Sunnyvale, CA

Barker, D.L.

Rapid, High Throughput DNA Sequencing Using Confocal Fluorescence Imaging of Capillary Arrays, 379

Monterey Bay Aquarium, Pacific Grove, CA

Pliskaln, C.H.

A New Instrument for Measuring Sinking Rates of Marine Particulates In Situ, 590

Morehouse School of Medicine, Atlanta, GA

Crandall, L.A.

Impact of Technology Derived from the Human Genome Project on Genetic Testing, Screening, and Counseling: Cultural, Ethical, and Legal Issues, 380

Imara, M.

Impact of Technology Derived from the Human Genome Project on Genetic Testing, Screening, and Counseling: Cultural, Ethical, and Legal Issues, 380

Moseley, R.E.

Impact of Technology Derived from the Human Genome Project on Genetic Testing, Screening,

and Counseling: Cultural, Ethical, and Legal Issues, 380

Phoenix, D.

Impact of Technology Derived from the Human Genome Project on Genetic Testing, Screening, and Counseling: Cultural, Ethical, and Legal Issues, 380

Trotter, R.W.

Impact of Technology Derived from the Human Genome Project on Genetic Testing, Screening, and Counseling: Cultural, Ethical, and Legal Issues, 380

Mount Sinai School of Medicine, New York, NY

Osman, R.

Theoretical Studies of Molecular Mechanisms in Radiation Damage to DNA, 200

Weinstein, H.

Theoretical Studies of Molecular Mechanisms in Radiation Damage to DNA, 200

National Academy of Sciences, Washington, DC

Abbott, S.B.

Polar Research Board, 757

Polar Research Board, 592

Katsouros, M.H.M.

Ocean Studies Board, 861

Support of the Ocean Studies Board, 591

Perry, J.S.

Board on Atmospheric Sciences and Climate, 758

National Academy of Sciences Institute of Medicine, Washington, DC

Bulger, R.E.

Predicting Future Disease: Issues in the Development, Application, and Use of Tests for Genetic Disorders, 381

National Aeronautics and Space Administration, Greenbelt, MD

Spinhrne, J.

Cirrus and Aerosol Profiler for Radiometric Measurements, 809

Wiscombe, W.J.

Theoretical Cloud Radiation Studies in Support of the Atmospheric Radiation Measurements Program, 810

National Aeronautics and Space Administration, New York, NY

Del Genio, A.D.

Observational Analysis of Climate Feedbacks and Trends, 808

Fung, I.Y.-S.

Spatial and Temporal Patterns of Biotic Exchanges of CO₂ Between the Atmosphere and Tropical Landscapes and Their Role in the Global Carbon Balance, 843

National Center for Atmospheric Research, Boulder, CO

Chervin, R.M.

Scientific Development of a Massively Parallel Ocean Climate Model, 759

Hack, J.J.

Improvement in Moist and Radiative Processes in Highly Parallel Atmospheric General Circulation Models: Validation and Development Through the CHAMMP Program, 760

Heymsfield, A.J.

Development and Testing of Parameterizations for Continental and Tropical Ice Cloud Microphysical and Radiative Properties in General Circulation and Mesoscale Models, 812

Kiehl, J.T.

A Hierarchical Approach to Improved Cloud-Radiation Parameterizations for Climate Models Through the Atmospheric Radiation Measurement Program, 811

Kropfli, R.A.

Shipboard Measurements of the Cloud-Capped Marine Boundary Layer During Fire/Atlantic Stratocumulus Transition Experiment, 813

Meehl, G.

Enhanced Research Program on the Long-Range Climatic Effects of Increasing Atmospheric Carbon Dioxide, 761

Washington, W.M.

Enhanced Research Program on the Long-Range Climatic Effects of Increasing Atmospheric Carbon Dioxide, 761

National Climatic Data Center, Asheville, NC

Karl, T.R.

Climatological Aerological (Upper Air) Reference Data Set, 763

Data Preparation and Analysis for Annex III, U.S./People's Republic of China Cooperation in the Field of Atmospheric Trace Gases, 762

National Council on Radiation Protection and Measurements, Bethesda, MD

Meinhold, C.

Development of Recommendations on Radiation Protection and Measurements, 243

National Environment Research Council, Surrey
GUS SUB United Kingdom

Pasham, Jr., M.

Simulations of the Carbon Cycle in the Oceans, 844

National Institute of Environmental Health Science,
Research Triangle Park, NC

Eldarov, M.

Genetic Analysis of Yeast Artificial Chromosome
 Following Yeast Transformation and Mitotic
 Growth, 303

Kouprina, N.

Genetic Analysis of Yeast Artificial Chromosome
 Following Yeast Transformation and Mitotic
 Growth, 303

Larionov, V.

Genetic Analysis of Yeast Artificial Chromosome
 Following Yeast Transformation and Mitotic
 Growth, 303

National Institute of Standards and Technology,
Gaithersburg, MD

Caswell, R.S.

Neutron Interactions with Biological Tissue, 201

Radon: Energy Deposition and Radiation Quality of
 Radon and Radon Daughters, 244

Costrell, L.

Instrumentation for Nuclear Applications, 245

Coyne, J.J.

Neutron Interactions with Biological Tissue, 201

Disdaroglu, M.M.

Ionizing Radiation-Induced DNA Damage and Its
 Repair in Human Cells, 172

Hutchinson, J.M.R.

Atom Counting Standards and Doppler Free
 RIMS, 246

Karam, L.R.

Radon: Energy Deposition and Radiation Quality of
 Radon and Radon Daughters, 244

Lucatorto, T.B.

Atom Counting Standards and Doppler Free
 RIMS, 246

Seltzer, S.

Electron Transport Calculations with Biomedical
 and Environmental Applications, 202

National Institutes of Health, Bethesda, MD

Cassett, J.

GenBank: The Genetic Sequence Data Bank, 382

National Institutes of Mental Health,
Washington, DC

Polymeropoulos, M.H.

Chromosomal Localization of Brain cDNAs, 383

National Oceanic and Atmospheric Administration,
Oak Ridge, TN

Hosker, Jr., R.P.

Atmospheric Turbulence and Diffusion
 Research, 566

Complex Topography in Atmospheric Studies in
 Complex Terrain, 567

National Renewable Energy Laboratory, Golden, CO

Hulstrom, R.L.

Atmospheric Radiation Measurements Program
 Support, 787

National Science Foundation, Washington, DC

Anderson, P.A.

CEES Working Group on Global Change, 764

West, R.

University National Oceanographic Laboratory
 System, 593

Naval Postgraduate School, Monterey, CA

Semtner, A.J.

Scientific Development of a Massively Parallel
 Ocean Climate Model, 765

Nebraska, University of, Lincoln, NE

Katz, R.

Theory of Relative Biological Effectiveness, 203

Nebraska Medical Center, University of, Omaha, NE

Leichner, P.K.

Dosimetry & Quantitative Radionuclide Imaging
 in Radioimmunotherapy, 518

Nevada, University of, Las Vegas, NV

Amy, P.S.

Spatial Variability of Deep Subsurface Micro-
 Organisms and Correlation with Hydrogeologic
 Parameters, 670

Jacobson, R.J.

Spatial Variability of Deep Subsurface Micro-
 Organisms and Correlation with Hydrogeologic
 Parameters, 670

Russell, C.E.

Spatial Variability of Deep Subsurface Micro-
 Organisms and Correlation with Hydrogeologic
 Parameters, 670

Wharton, R.A.

Spatial Variability of Deep Subsurface Micro-
 Organisms and Correlation with Hydrogeologic
 Parameters, 670

New Hampshire, University of, Durham, NH

Moore, III, B.

Spatial and Temporal Patterns of Biotic Exchanges
 of CO₂ Between the Atmosphere and Tropical

Landscapes and Their Role in the Global Carbon Balance, 845

Skole, D.L.

Spatial and Temporal Patterns of Biotic Exchanges of CO₂ Between the Atmosphere and Tropical Landscapes and Their Role in the Global Carbon Balance, 845

New Mexico School of Medicine, University of, Albuquerque, NM

Samet, J.M.

Lung Cancer Epidemiology in New Mexico Uranium Miners, 93

Lung Cancer in Uranium Miners—A Tissue Resource, 94

New Mexico Institute of Mining and Technology, Socorro, NM

Kleff, T.L.

Water Potential in Relation to Numbers and Activities of Microbes in Saturated and Unsaturated Subsurface Environments, 671

Phillips, F.M.

A Geological Approach to Characterizing Aquifer Heterogeneity, 673

Mathematical and Geological Approaches to Minimizing the Data Requirements for Statistical Analysis of Hydraulic Conductivity Distributions, 672

Schery, S.D.

Transport of Radon and Thoron at the Earth's Surface, 675

Wilson, J.L.

A Geological Approach to Characterizing Aquifer Heterogeneity, 673

Mathematical and Geological Approaches to Minimizing the Data Requirements for Statistical Analysis of Hydraulic Conductivity Distributions, 672

Small Scale Laboratory Studies of Flow and Transport Phenomena in Pores and Fractures: Phase II, 674

New York University, New York, NY

Broyde, S.

Molecular Understanding of Mutagenicity Using Potential Energy Methods, 173

Geacintov, N.E.

Base Sequence Effects on Interactions Between Aromatic Mutagens and DNA, 174

Mechanisms of Interaction of Radiation with Matter, 204

Hoffert, M.I.

Climate Evolution with a Coupled Two-Dimensional Atmospheric/Ocean Model, 766

Cloud and Ocean Effects on Greenhouse Warming, 814

Pope, M.

Mechanisms of Interaction of Radiation with Matter, 204

New York University Medical Center, New York, NY

Cohen, B.S.

Particle Deposition in Human and Canine Tracheobronchial Casts, 96

Harley, N.H.

Measurement and Apportionment of Radon Source Terms for Modeling Indoor Environments, 97

Robbins, E.S.

Cellular Morphometry of the Bronchi of Human and Dog Lungs, 95

North Carolina, University of, at Chapel Hill, Chapel Hill, NC

Benninger, L.K.

Carbon Cycling on the Continental Margin: Evidence from Sediment ¹⁴C and Nutrient Elements, 594

Misra, R.

Development of Human Viral-Based Genomic Library of 150 to 200 Kb Inserts, 386

Sun, T.Q.

Development of Human Viral-Based Genomic Library of 150 to 200 Kb Inserts, 386

Vos, J.M.H.

Development of Human Viral-Based Genomic Library of 150 to 200 Kb Inserts, 386

North Carolina State University, Raleigh, NC

Pietrafesa, L.J.

A Study of Sediment Motions and Bottom Boundary Layer Dynamics Over the Mid-Atlantic Bight Shelf and Upper Slope, 595

Northeastern University, Boston, MA

Giese, R.W.

New Fluorescence Methodology for Detecting DNA Adducts, 247

Karger, B.L.

The Separation of DNA by Pulsed Field Capillary Electrophoresis, 387

University of Notre Dame, Notre Dame, IN

Babic, M.

Hydrodynamic Controls on Particle Transport Through Heterogeneous Porous Media, 676

Silliman, S.E.

Hydrodynamic Controls on Particle Transport Through Heterogeneous Porous Media, 676

**Oak Ridge Institute for Science and Education,
Oak Ridge, TN**

Adler, H.I.

Microbiology, 141

Boyle, W.R.

Technical Assistance for Committee on Interagency
Radiation Research and Policy Coordination, 51

Holmes, L.

Human Genome Distinguished Postdoctoral
Fellowships, 313

Postdoctoral Research Program for Global Change, 824

McCamant, L.

Alexander Hollaender Distinguished Postdoctoral
Fellowships, 53

McCleary, D.

OHER/Historically Black Colleges and
Universities Faculty and Student Research
Participation Program, 54

Minner, D.

Technical Support for Implementation of the DOE
Human Subject Policy, 52

Snyder, F.

Alterations in Lipid Metabolism, Cell Mediators, and
Membranes in Disease, 142

Watson, E.E.

Radiopharmaceutical Internal Dose Information
Center, 476

Wohlpert, A.

Alexander Hollaender Distinguished Postdoctoral
Fellowships, 53

Human Genome Distinguished Postdoctoral
Fellowships, 313

OHER/Historically Black Colleges and
Universities Faculty and Student Research
Participation Program, 54

Oak Ridge National Laboratory, Oak Ridge, TN

Adamson, A.E.

Human Genome Management Information System, 322

Allison, D.P.

Using Scanning Tunneling Microscopy to Sequence the
Human Genome, 315

Ambrose, K.R.

Nuclear Medicine and Biomedical Radioisotope
Technology, 478

Arakawa, E.T.

Physics of Solids and Macromolecules, 182

Arlinghaus, F.

DNA Sequencing Using Stable Isotopes, 317

Bales, R.C.

Mobility of Microorganisms in a Sandy Aquifer, 636

Blaylock, B.G.

Radionuclides in the Environment, 630

Brown, G.M.

Detection of Luminescence from Lanthanide Ions as
Labels for DNA Sequencing, 314

DNA Sequencing Using Stable Isotopes, 317

Using Scanning Tunneling Microscopy to Sequence the
Human Genome, 315

Buchanan, M.V.

Isomers and Interactables: Identification of
Bio-Adducts, 223

Buckner, M.A.

Radiation Calibration Laboratory, 227

Bunick, G.J.

Structural Biology of Nucleosomes, 436

Burlage, R.S.

Mobility of Microorganisms in a Sandy Aquifer, 636

Callahan, A.P.

Biomedical Radioisotope Technology Development, 479
Nuclear Medicine and Biomedical Radioisotope
Technology, 478

Calcott, T.A.

Physics of Solids and Macromolecules, 182

Carman, Jr., H.S.

Chemical Physics Studies in the Gaseous and
Liquid Phases, 186
Ion Chemistry and Molecular Clustering
Phenomena, 189

Carter, J.G.

Electron-Molecule Interactions, 185

Casey, D.K.

Human Genome Management Information System, 322

Casson, W.H.

Radiation Calibration Laboratory, 227

Caton, G.M.

Radon Information Transfer, 64

Chen, C.H.

Chemical Kinetics of Irradiated Materials, 183
Resonance Ionization Spectroscopy, 225
Vacuum Ultraviolet Ionizer Mass Spectrometer for
Genome Sequencing, 321

Christophorou, L.G.

Atomic, Molecular, and Interphase Physics, 184
Electron-Molecule Interactions, 185

Compton, R.N.

Chemical Physics Studies in the Gaseous and Liquid
Phases, 186
Ion Chemistry and Molecular Clustering Phenomena, 189
Nanosecond and Picosecond Nonlinear Laser
Techniques, 226

Cook, J.S.

Regulation of Membrane Transport, 143

Cristy, M.

Medical Physics and Internal Dosimetry, 224

Cushman, R.

Database Support to Assist in Quantifying the
Link Between Changes in Atmospheric Composition
and Climate Change, 788

Carbon Dioxide Information Analysis Center, 825

Carbon Dioxide Information and Analysis Research
Program: Resource Analysis, 826

Davidson, J.B.

Genomic Instrumentation Development:

Detection Systems for Film and High Speed

Gel-Less Methods, 323

Davidson, K.A.

Human Genome Management Information System, 322

Dudney, C.S.

Investigation of Radon Entry and Effectiveness of
Mitigation Measures, 639

Eckerman, K.F.

Medical Physics and Internal Dosimetry, 224

Emanuel, W.R.

Carbon Cycle Program Management, 827

Ferrell, T.L.

Liquid and Submicron Physics, 187

Using Scanning Tunneling Microscopy to Sequence
the Human Genome, 315

Foote, R.S.

Protein Engineering and Molecular Mutagenesis, 146

DNA Sequence Analysis by Solid-Phase

Hybridization, 316

Detection of Luminescence from Lanthanide Ions as
Labels for DNA Sequencing, 314

Genomic Instrumentation Development:

Detection Systems for Film and High Speed

Gel-Less Methods, 323

DNA Sequencing Using Stable Isotopes, 317

Frank, M.L.

Radionuclides in the Environment, 630

Frome, E.L.

Biostatistics and Biomathematics, 63

Gammage, R.B.

Dosimetry for New Energy Systems Pollutants, 229

Investigation of Radon Entry and Effectiveness of
Mitigation Measures, 639

Gardner, R.H.

System Processes in Landscape Ecology, 699

Garrett, W.R.

Chemical Kinetics of Irradiated Materials, 183

Resonance Ionization Spectroscopy, 225

Garten, C.T.

Walker Branch Watershed Project, 700

Generoso, E.

Generating a Comparative Physical Map of
Mouse Chromosome 7, 319

Generoso, W.M.

Mammalian Chemical Mutagenesis Program, 55

Effects and Uses of Chromosome Aberrations, 144

Mammalian Genetics, 57

Grebmeier, J.M.

Radionuclides in the Coastal Zone, 702

Griffin, G.D.

Dosimetry for New Energy Systems Pollutants, 229

Hamm, R.N.

Microdosimetry, Biological Modeling, and
Theoretical Biophysics, 188

Pulse-Characterization Neutron Dosimetry, 228

Harpel, M.R.

Protein Chemistry, 145

Hartman, F.C.

Protein Chemistry, 145

Protein Engineering and Molecular Mutagenesis, 146

Herbes, S.E.

Mixed-Waste Biodegradation, 637

Hettich, R.L.

Isomers and Interactables: Identification of
Bio-Adducts, 223

Hoffman, F.O.

Radionuclides in the Environment, 630

Hurst, G.B.

Isomers and Interactables: Identification of
Bio-Adducts, 223

Huston, M.A.

Walker Branch Watershed Project, 700

Jacobs, G.K.

Soil-Water-Contaminant Interactions, 631

Jacobson, K.B.

Detection of Luminescence from Lanthanide Ions as
Labels for DNA Sequencing, 314

DNA Sequence Analysis by Solid-Phase
Hybridization, 316

DNA Sequencing Using Stable Isotopes, 317

Using Scanning Tunneling Microscopy to Sequence the
Human Genome, 315

Vacuum Ultraviolet Ionizer Mass Spectrometer for
Genome Sequencing, 321

Jardine, P.M.

Characterization and Microbial Utilization of Organic
Carbon, 635

Colloidal Mobility Experiments Using Natural
Organics, 634

Field-Scale Validation of Multispecies Transport, 633

Soil-Water-Contaminant Interactions, 631

- Subsurface Transport Model Validation and Uncertainty Analysis in Heterogeneous Field Soils, 632
- Kanciruk, P.**
Database Support to Assist in Quantifying the Link Between Changes in Atmospheric Composition and Climate Change, 788
- Kerr, G.D.**
Medical Physics and Internal Dosimetry, 224
- Kennel, S.J.**
Monoclonal Antibodies for Study of Metastases, 477
- Klots, C.E.**
Chemical Physics Studies in the Gaseous and Liquid Phases, 186
Ion Chemistry and Molecular Clustering Phenomena, 189
- Knapp, Jr., F.F.**
Biomedical Radioisotope Technology Development, 479
Nuclear Medicine and Biomedical Radioisotope Technology, 478
- Kocher, D.C.**
Medical Physics and Internal Dosimetry, 224
- Kryter, R.C.**
Widely Deployable Low Cost Radiometer for the Atmospheric Radiation Measurement Program Extended Observing Stations, 789
- Larimer, F.W.**
Protein Engineering and Molecular Mutagenesis, 146
Detection of Luminescence from Lanthanide Ions as Labels for DNA Sequencing, 314
DNA Sequencing Using Stable Isotopes, 317
- Larsen, I.L.**
Radionuclides in the Coastal Zone, 702
- Leggett, R.W.**
Medical Physics and Internal Dosimetry, 224
- Lee, S.Y.**
Mixed-Waste Biodegradation, 637
- Liang, L.**
Colloidal Mobility Experiments Using Natural Organics, 634
- Lindberg, S.E.**
Atmosphere-Canopy Interactions, 552
- Lu, P.Y.**
Radon Information Transfer, 64
- Mansfield, B.K.**
Human Genome Management Information System, 322
- Martin, S.A.**
Human Genome Management Information System, 322
- Mazur, P.**
Theoretical and Applied Cryobiology, 147
- McCarthy, J.F.**
Characterization and Microbial Utilization of Organic Carbon, 635
Colloidal Mobility Experiments Using Natural Organics, 634
Mobility of Microorganisms in a Sandy Aquifer, 636
- McPherson, D.W.**
Nuclear Medicine and Biomedical Radioisotope Technology, 478
- Miller, J.C.**
Chemical Physics Studies in the Gaseous and Liquid Phases, 186
Ion Chemistry and Molecular Clustering Phenomena, 189
Nanosecond and Picosecond Nonlinear Laser Techniques, 226
Chemical Kinetics of Irradiated Materials, 183
Resonance Ionization Spectroscopy, 225
- Mirzadeh, S.**
Biomedical Radioisotope Technology Development, 479
Nuclear Medicine and Biomedical Radioisotope Technology, 478
- Mitra, S.**
Mutations in Shuttle Plasmids, 62
Protein Engineering and Molecular Mutagenesis, 146
Protein-Nucleic Acid Interactions, 148
- Mucenski, M.L.**
Mapping in Mouse-Human Homologous Regions, 318
- Mulholland, P.J.**
Walker Branch Watershed Project, 700
- Mural, R.J.**
Mapping in Mouse-Human Homologous Regions, 318
Protein Engineering and Molecular Mutagenesis, 146
- Niyogi, S.K.**
Protein Engineering and Molecular Mutagenesis, 146
Protein-Nucleic Acid Interactions, 148
- Norby, L.**
Elevated Carbon Dioxide Effects on Woody Plant Soil Systems, 828
- Nyquist, J.E.**
Investigation of Radon Entry and Effectiveness of Mitigation Measures, 639
- O'Neill, R.V.**
System Processes in Landscape Ecology, 699
- Olins, D.E.**
Chromosome Chemistry, 437

Palumbo, A.V.

Characterization and Microbial Utilization of Organic Carbon, 635

Mixed-Waste Biodegradation, 637

Mobility of Microorganisms in a Sandy Aquifer, 636

Parr, P.D.

National Environmental Research Park, 701

Payne, M.G.

Resonance Ionization Spectroscopy, 225

Vacuum Ultraviolet Ionizer Mass Spectrometer for Genome Sequencing, 321

Peng, T.-H.

Oceanic Uptake of Carbon Dioxide, 856

Phelps, T.J.

Subsurface Microbial Ecology of GEMHEX and Triassic Basin Samples, 638

Popp, R.A.

Flow Cytometric Data Analysis, 149

Mammalian Biochemical Genetics, 56

Ramsey, R.S.

Detection of Luminescence from Lanthanide Ions as Labels for DNA Sequencing, 314

Rinchik, E.M.

Generating a Comparative Physical Map of Mouse Chromosome 7, 319

Mammalian Genetics, 57

Mapping in Mouse-Human Homologous Regions, 318

Molecular Analysis of Mouse Mutations, 150

Ritchie, R.H.

Microdosimetry, Biological Modeling, and Theoretical Biophysics, 188

Transport and Surface Physics, 190

Russell, L.B.

Freezing Mouse Mutants, 58

Mammalian Chemical Mutagenesis Program, 55

Mammalian Genetics, 57

Mapping in Mouse-Human Homologous Regions, 318

Sachleben, R.A.

Detection of Luminescence from Lanthanide Ions as Labels for DNA Sequencing, 314

DNA Sequence Analysis by Solid-Phase Hybridization, 316

DNA Sequencing Using Stable Isotopes, 317

Sauers, I.

Physics of Solids and Macromolecules, 182

Sega, G.A.

Mammalian Chemical Mutagenesis Program, 55

Selby, P.B.

Genetics Hazards of Radiation, 59

Mammalian Genetics, 57

Sims, C.S.

Radiation Calibration Laboratory, 227

Sincovec, R.F.

Biostatistics and Biomathematics, 63

Computational Support for Parallel Climate Modeling, 735

Skinner, D.M.

Growth and Regeneration in a Land Crab Model System, 151

Srivastava, P.C.

Nuclear Medicine and Biomedical Radioisotope Technology, 478

Radiolabeled Nucleoside Probes for Tumor Diagnosis, 480

Stevens, A.

Protein-Nucleic Acid Interactions, 148

Stinnett, D.B.

Human Genome Management Information System, 322

Stubbs, L.J.

Mapping in Mouse-Human Homologous Regions, 318

Generating a Comparative Physical Map of Mouse Chromosome 7, 319

Terzaghi-Howe, M.

Mechanisms in Radiation Carcinogenesis, 60

The Carcinogenic Effects of Alpha-Particle Radiation on Tracheal Cells, 61

Thonnard, N.

DNA Sequencing Using Stable Isotopes, 317

Thundat, T.G.

Using Scanning Tunneling Microscopy to Sequence the Human Genome, 315

Toran, L.

Mixed-Waste Biodegradation, 637

Turner, J.E.

Microdosimetry, Biological Modeling, and Theoretical Biophysics, 188

Pulse-Characterization Neutron Dosimetry, 228

Turner, M.G.

System Processes in Landscape Ecology, 699

Uberbacher, E.C.

ORAIL: An Intelligent System for DNA Sequence Analysis, 320

Mapping in Mouse-Human Homologous Regions, 318

Uziel, M.

Dosimetry for New Energy Systems Pollutants, 229

Vo-Dinh, T.

Dosimetry for New Energy Systems Pollutants, 229

Von Damm, K.L.

Radionuclides in the Coastal Zone, 702

Ward, R.C.

Parallel Atmospheric Climate Model, 734

Warmack, R.J.

Liquid and Submicron Physics, 187

Using Scanning Tunneling Microscopy to Sequence the Human Genome, 315

Wassom, J.S.

Human Genome Management Information System, 322

Waters, L.C.

Mutations in Shuttle Plasmids, 62

Williams, T.M.

Mobility of Microorganisms in a Sandy Aquifer, 636

Wilson, D.L.

Investigation of Radon Entry and Effectiveness of Mitigation Measures, 639

Wilson, V.

Subsurface Transport Model Validation and Uncertainty Analysis in Heterogeneous Field Soils, 632

Woychik, R.P.

DNA Sequencing Using Stable Isotopes, 317

Insertional Mutagenesis and Gene Analysis, 152

Mapping in Mouse-Human Homologous Regions, 318

Detection of Luminescence from Lanthanide Ions as Labels for DNA Sequencing, 314

Wyrick, J.M.

Human Genome Management Information System, 322

Yang, W.K.

Carcinogen-Cell Genome Interaction, 153

Yust, L.N.

Human Genome Management Information System, 322

Oakland University, Rochester, MI

Sevilla, M.D.

Mechanisms for Radiation Damage in DNA, 98

Ocean Optics, Inc., Dunedin, FL

Morris, M.J.

Inherently Calibrated Fiber Optic Sensors for Measuring Seawater pH, 596

Walters, R.A.

A Multiaperture Optical System for In Situ Measurement of the Flux and Sinking Speed of Marine Snow Aggregates, 597

Ohio State University, Columbus, OH

Barth, R.E.

Synthesis and Evaluation of Boron Compounds for Neutron Capture Therapy of Malignant Brain Tumors, 519

Soloway, A.H.

Synthesis and Evaluation of Boron Compounds for Neutron Capture Therapy of Malignant Brain Tumors, 519

Ohio State University Research Foundation, Columbus, OH

Blue, T.E.

An Accelerator Neutron Source for Boron Neutron Capture Therapy, 520

Everett, K.R.

Hydrological and Geochemical Response and Recovery in Disturbed Arctic Ecosystems, 715

Oregon, University of, Charleston, OR

Shapiro, L.P.

Controls on Marine Carbon Fluxes via Phytoplankton: Microzooplankton Interactions in Continental Shelf Waters, 599

Oregon, University of, Eugene, OR

Wood, A.M.

Phytoplankton Excretion Revisited: Healthy Cells May Not Do It, But How Many Cells Are Healthy?, 598

Oregon Graduate Center, Beaverton, OR

Fish, W.

Adsorption of Chromate/Organic Acid Waste Mixtures in Aquifer Materials, 677

Palmer, C.D.

Adsorption of Chromate/Organic Acid Waste Mixtures in Aquifer Materials, 677

Oregon Graduate Institute of Science and Technology, Beaverton, OR

Khalil, M.A.K.

Methane Fluxes from Rice Fields in China: Spatial and Temporal Variability and Estimates of Contributions to the Global Budget, 767

Rasmussen, R.A.

Methane Fluxes from Rice Fields in China: Spatial and Temporal Variability and Estimates of Contributions to the Global Budget, 767

Oregon State University, Corvallis, OR

Sherr, B.F.

Controls on Marine Carbon Fluxes via Phytoplankton: Microzooplankton Interactions in Continental Shelf Waters, 599

Pacific Northwest Laboratories, Richland, WA

Ainsworth, C.C.

Chemical Desorption, Dissolution, and Partitioning, 646

Allwine, K.J.

Atmospheric Diffusion in Complex Terrain, 553

- Barchet, W.R.**
DOE Atmospheric Chemistry Program
Management, 554
North Atlantic Regional Experiment Field
Campaign, 555
- Berkowitz, C.M.**
Continental and Oceanic Fate/Air Pollutants, 556
- Bolton, Jr., H.**
Chemistry/Microbiology Controlling Chelated
Radionuclide Transport, 648
Microbial Sequestration and Bioaccumulation of
Radionuclides and Metals, 647
- Braby, L.A.**
Radiation Dosimetry, 191
Biological Effectiveness of Radon Alpha
Particles, 231
- Brockman, F.J.**
Chemical Remediation Concepts: Bioremediation
Concepts, 644
- Brooks, A.L.**
Genotoxicity of Inhaled Energy Effluents, 66
In Vivo/In Vitro Radon-Induced Cellular Damage, 67
Low-Level $^{239}\text{PuO}_2$ Lifespan Studies, 65
- Bushaw, B.A.**
Determination of Radon Exposure: Laser
Measurements of ^{210}Pb , 230
- Busness, K.M.**
Research Aircraft Operations, 557
- Cross, F.T.**
Mechanisms of Radon Injury, 69
Radon Hazards in Homes, 68
- Doran, J.C.**
Atmospheric Studies in Complex Terrain Program:
Scientific Direction, 558
Direct Simulation of Atmospheric Turbulence, 559
Point-Area Relationships for Global Climate
Modeling, 791
- Douhart, R.J.**
GnomeView: A Graphical Interface to the Human
Genome, 325
- DuBois, R.D.**
Radiation Physics, 192
- Edmonds, C.G.**
Ion Cyclotron Resonance Mass Spectroscopy of
DNA Molecular Ions, 324
- Fredrickson, J.F.**
Subsurface Microbial Phenomena, 640
- Fredrickson, J.K.**
Deep Subsurface Microbiological Investigations, 641
- Fruchter, J.S.**
Manipulation of Natural Subsurface Processes: Field
Research and Validation, 645
- Fuclarelli, A.F.**
Biochemistry of Free Radical-Induced DNA
Damage, 70
- Gee, G.W.**
Radon Transport Modeling in Soils, 643
- Ghan, S.J.**
Development of a General Circulation Model
Stratiform Cloud Parameterization, 794
- Girvin, D.C.**
Chemistry/Microbiology Controlling Chelated
Radionuclide Transport, 648
- James, A.C.**
Aerosol Technology Development, 71
Microdosimetry of Radon Daughters, 72
- Laulainen, N.S.**
Network-Based Solar and Meteorological
Characterization of Cloud-Radiation Effects
in Global Climate Modeling, 792
- Long, P.E.**
Deep Microbiology Geosciences Testing, 649
Microbial Origin/Transport in Subsurface
Systems, 651
- Loo, J.A.**
Ion Cyclotron Resonance Mass Spectroscopy of
DNA Molecular Ions, 324
- Kennedy, R.A.**
Chernobyl Database, 232
- Mahaffey, J.A.**
Chernobyl Database, 232
- McKinley, J.P.**
Pore Water Chemistry, 650
- Miller, R.J.**
Lasers in Environmental Research, 233
- Miller, J.H.**
Modeling Cellular Responses to Genetic
Damage, 193
- Murphy, E.M.**
Microbial Origin/Transport in Subsurface
Systems, 651
- Nelson, J.M.**
Radiation Biophysics, 194
- Park, J.F.**
Inhaled Plutonium Oxide in Dogs, 73
- Pelkey, J.E.**
GnomeView: A Graphical Interface to the Human
Genome, 325
- Rawson, S.A.**
Deep Microbiology Geosciences Testing, 649
- Rogers, L.E.**
Dynamics of Arid Land Ecosystems, 703
Environmental Research Park, 704

Schneider, R.P.

Mutation of DNA Targets, 74

Shaw, W.J.

Interactions Between Surface Exchange Processes and Atmospheric Circulations, 560

Sikov, M.R.

Fetal and Juvenile Radiotoxicity, 75

Simmons, C.S.

Subsurface Organic Fluid Flow, 652

Slinn, W.G.N.

Parameterizations for Integrals of Radiation's Effects on Clouds, Surfaces, and Stabilities, 795

Smith, R.D.

Capillary Electrophoresis Mass Spectrometry for DNA Adducts, 234

Ion Cyclotron Resonance Mass Spectroscopy of DNA Molecular Ions, 324

Springer, D.L.

Molecular Events During Tumor Initiation, 76

Stiegler, G.L.

Oncogenesis in Radiation Carcinogenesis, 77

Stokes, G.M.

Atmospheric Radiation Measurement Program, 790

Strelle, G.P.

Intermediate Scale Subsurface Transport of Co-Contaminants, 653

Szecsody, J.E.

Intermediate Scale Subsurface Transport of Co-Contaminants, 653

Thomas, J.M.

Designs for Environmental Field Studies, 705

Thurman, D.A.

GnomeView: A Graphical Interface to the Human Genome, 325

Watson, C.

National Radiobiology Archives, 78

Whiteman, C.D.

Coupling/Decoupling of Local and Synoptic Circulations, 561

Photometric Studies of Clouds from an Atmospheric Radiation Measurement Program Site, 793

Wildung, R.E.

Chemical Desorption, Dissolution, and Partitioning, 646

Chemical Remediation Concepts: Bioremediation Concepts, 644

Manipulation of Natural Subsurface Processed: Field Research and Validation, 645

Microbial Sequestration and Bioaccumulation of Radionuclides and Metals, 647

Wood, B.D.

Microbial Origin/Transport in Subsurface Systems, 651

Zachara, J.M.

Manipulation of Natural Subsurface Processed: Field Research and Validation, 645

Subsurface Chemistry of Organic Chemical and Organic Radionuclide Mixtures, 642

Pacific Northwest Laboratory, Sequim, WA

Denbo, D.W.

Ocean Convection Parameterization, 736

Downing, J.P.

Carbon Dioxide Ocean Research, 857

Pacific Northwest Laboratory, Washington, DC

Edmonds, J.A.

Resource Analysis Research, 830

Energy and Future Carbon Dioxide Emissions, 829

Scott, M.

Resource Analysis Research, 830

Pennsylvania, University of, Philadelphia, PA

Karp, J.

Positron Ring System Using Angle-Type Detectors, 521

Searls, D.B.

Foundation for a Syntactic Pattern Recognition System for Genomic DNA Sequences, 388

Pennsylvania State University, University Park, PA

Castleman, Jr., A.W.

Clusters: Elucidating the Dynamics of Ionization Events and Ensuing Reactions in the Condensed Phase, 205

Radon: Chemical and Physical Processes Associated with Its Distribution and Effects, 248

Rose, A.W.

Generation and Mobility of Radon in Soil, 679

Winograd, N.

Characterization of Carcinogenic Materials Using Ion Beams and Lasers, 249

Yeh, G.T.

Field-Scale Validation and Development of a Three-Dimensional Fluid Flow and Multispecies-Hydrogeochemical Transport Model, 678

Physical Sciences, Inc., Andover, MA

Marinelli, W.J.

An Imaging Fabry-Perot Spectrometer for Site Evaluation of Trace Species, 680

An Imaging Fabry-Perot Spectrometer for Site Evaluation of Trace Species, 250

Pittsburgh, University of, Pittsburgh, PA

Aker, P.M.

Characterization of Gas-Aerosol Interaction Kinetics Using Morphology-Dependent Stimulated Raman Scattering, 568

Princeton University, Princeton, NJ

Gruner, S.M.

Development and Applications of Photo-Sensitive Device Systems to Studies of Biological and Organic Materials, 442

Pacala, S.W.

A Theory of Forest Dynamics: Spatially Explicit Models and Issues of Scale, 716

Sarmiento, J.L.

Simulations of the Carbon Cycle in the Oceans, 846

Princeton University, School of Engineering and Applied Science, Princeton, NJ

Socolow, R.H.

Exposure to Radon and Radon Progeny in the Indoor Environment, 251

Suckewer, S.

Reflection Imaging X-Ray Laser Microscope and Its Biological Applications, 252

Promega Corporation, Madison, WI

Lowery, R.

Site-Specific Endonucleases for Human Genome Mapping, 389

Purdue Research Foundation, West Lafayette, IN

Cushman, J.H.

Supercomputer Simulation of Clay-Chemical-Water Interactions: Phase III, 681

Ransom Hill Bioscience, Ramona, CA

MacDonnell, M.T.

High Speed Electrophoresis in a Solid Substrate, 390

Rensselaer Polytechnic Institute, Troy, NY

Nierzwicki-Bauer, S.A.

Phylogenetic Relationships Among Subsurface Micro-Organisms, 682

Rhode Island Hospital and Brown University, Providence, RI

Jackson, C.L.

An Improved Method for Producing Radiation Hybrids Applied to Human Chromosomes, 391

Mark, H.F.L.

An Improved Method for Producing Radiation Hybrids Applied to Human Chromosomes, 391

Rice University, Houston, TX

Rorschach, H.E.

Quasi-Elastic Neutron-Scattering Studies of Protein Dynamics, 443

Rochester, University of, Rochester, NY

Muenter, J.S.

Intermolecular Potential Functions from Spectroscopic Properties of Weakly Bound Complexes, 206

Rochester School of Medicine, University of, Rochester, NY

Lawrence, C.W.

Molecular Mechanisms of Misrepair Mutagenesis, 175

Prakash, L.

Excision Repair of Ultra-Violet Damaged DNA: Genes and Proteins of Yeast and Humans, 176

Rutgers University, New Brunswick, NJ

Avisar, R.

An Evaluation of the Appropriate Land-Surface Resolution for Climate Models, 768

SRI International, Menlo Park, CA

Rudd, C.

Analysis of Gene-Specific DNA Adduction by Energy-Related Chemicals, 101

Salk Institute for Biological Studies, The, La Jolla, CA

Wahl, G.

Isolation of Specific Human Telomeric Clones by Homologous Recombination and Yeast Artificial Chromosome Rescue, 392

Evans, G.A.

Technology Development for Physical Mapping of Human Chromosomes, 393

San Diego State University, San Diego, CA

Oechel, W.C.

Response of Tundra Ecosystems to Elevated Atmospheric Carbon Dioxide, 847

Sandia National Laboratory, Albuquerque, NM

Swissheim, J.

Parallel Methods for Climate Modeling, 737

Sandia National Laboratory, Livermore, CA

Kegelmeyer, Jr., P.W.

Passive Cloud Dynamics Measurement—A Flow Field Registration Approach, 797

Lapp, M.

Laser Remote Sensing of Water Vapor, 796

Melfi, S.H.

Laser Remote Sensing of Water Vapor, 796

Santa Fe Institute, Santa Fe, NM

Knapp, E.A.

A Broad Research Program on the Sciences of Complexity, 769

Savannah River Ecology Laboratory, Aiken, SC

Smith, M.H.

National Environmental Research Park, 706

Schepens Eye Research Institute, The, Boston, MA

Webb, R.H.

Center of Excellence—Microlaser
Microscope, 522

**Science Applications International Corp.,
San Diego, CA**

Byrne, R.N.

Evaluation of a New General Circulation Model-
Capable Stochastic Cloud/Radiation
Parameterization Using Atmospheric
Radiation Measurement Data, 815

Science Research Laboratory, Somerville, MA

Hughey, B.J.

A New High Yield Cryogenic Target for Fluorine-18
Production, 523

Scripps Institution of Oceanography, La Jolla, CA

Barnett, T.

Atmospheric Radiation Measurement Tropical Pacific
Experiment: Role of Cloud, Water Vapor and
Convection Feedbacks in the Coupled Ocean/
Atmosphere System, 816

Barnett, T.P.

Studies of Ocean Predictability at Decade to Century
Time Scales Using a Global Ocean General
Circulation Model in a Parallel Computing
Environment, 770

Birdsall, T.

Acoustic Global Warming Feasibility Experiment, 865

Dickson, A.G.

The Quality Control of Oceanic Carbon Dioxide
Measurements: Preparation and Distribution of
Reference Materials, 862

Keeling, C.D.

A Study of the Abundance and $^{13}\text{C}/^{12}\text{C}$ Ratio of
Atmospheric Carbon Dioxide and Oceanic
Carbon in Relation to the Global Carbon
Cycle, 848

Oceanic CO_2 Measurements for the World Ocean
Circulation Experiment Hydrographic Survey in
the Pacific Ocean, 1990-1991: Shore-Based
Analysis During LEG 1-3, 863

Oceanic CO_2 Measurements for the World Ocean
Circulation Experiment Hydrographic Survey of

the Pacific Ocean: Shipboard Alkalinity Analyses
During 1991 and 1992, 864

Miller, A.

Studies of Ocean Predictability at Decade to Century
Time Scales Using a Global Ocean General
Circulation Model in a Parallel Computing
Environment, 770

Munk, W.

Acoustic Global Warming Feasibility Experiment, 865

Ramanathan, V.

Central Equatorial Pacific Experiment, 866
Atmospheric Radiation Measurement Tropical
Pacific Experiment: Role of Cloud, Water Vapor
and Convection Feedbacks in the Coupled Ocean/
Atmosphere System, 816

Spindel, R.

Acoustic Global Warming Feasibility Experiment, 865

Weiss, R.R.

Measurements of Surface Ocean Carbon Dioxide
Partial Pressure During World Ocean
Circulation Experimentation, 867

Sea Tech, Inc., Corvallis, OR

Bartz, R.

Calibration of In Situ Optical Devices Using a Pure
Water Standard, 600
Development of a Spectral Attenuation Meter and a
Spectral Back Scattering Meter, 601

Skidaway Institute of Oceanography, Savannah, GA

Jahnke, R.A.

Burial, Remineralization, and Utilization of Organic
Matter at the Seafloor Under a Strong Western
Boundary Current, 602

Paffenhofer, G.

The Impact of Proto- and Metazooplankton on the
Fate of Organic Carbon in Continental Ocean
Margins, 603

**Sloan Kettering Memorial Cancer Center,
New York, NY**

Ling, C.C.

Activation of Oncogenes by Radon Progeny and
X Rays, 99

**Sloan-Kettering Institute for Cancer Research,
New York, NY**

Larson, S.M.

Biomedical Research with Cyclotron-Produced
Radionuclides, 524

Smithsonian Institution, Edgewater, MD

Drake, B.G.

A Field Study of the Effects of Elevated Ambient
 CO_2 on Ecosystem Processes in Chesapeake
Bay Wetlands, 849

South Carolina, University of, Columbia, SC**Lincoln, D.E.**Herbivore Responses to Plants Grown in Enriched CO₂ Atmosphere, 850**Mishra, N.C.**

Characterization of Mammalian DNA Polymerase Gene(s) and Protein(s), 177

Southern California, University of, Los Angeles, CA**Cortopassi, G.A.**

Direct Detection of Mutations in Human Mitochondrial and Nuclear DNA Using the Polymerase Chain Reaction, 100

Lambropoulos, P.

Theoretical Problems in Laser Spectroscopy of Atoms and Molecules, 253

Southern Methodist University, Dallas, TX**Gray, H.**

Statistical Examination of Climatological Data Relevant to Global Temperature Variations, 817

Gunst, R.

Statistical Examination of Climatological Data Relevant to Global Temperature Variations, 817

Woodward, W.

Statistical Examination of Climatological Data Relevant to Global Temperature Variations, 817

Southern Mississippi, University of, Stennis Space Center, MS**Lohrenz, S.E.**

Development of a Multisensor In Situ Fiber Optic Fluorometer, 604

Southwest Sciences, Inc., Santa Fe, NM**Stanton, A.C.**

Fast Response Instrumentation for Methane Flux Measurements, 569

Fast Response Instrumentation for Methane Flux Measurements, 254

Spectral Sciences, Inc., Burlington, MA**Goldstein, N.**

A Diode-Laser Absorption Remote Concentration Sensor, 255

A Diode-Laser Absorption Remote Concentration Sensor, 570

St. Mary's Hospital and Medical Center, Grand Junction, CO**Saccomanno, G.**

Early Lung Cancer Detection in Uranium Miners with Abnormal Sputum Cytology, 102

Stanford Linear Accelerator Center, Stanford, CA**Hodgson, K.O.**

Structural Molecular Biology Support Initiative, 438

Stanford University, Stanford, CA**Cavalli-Sforza, L.C.**

Human Genetic Diversity, 394

Roughgarden, J.

Theoretical Ecology of Marine Populations, 717

Stanford University School of Medicine, Stanford, CA**Rubenstein, E.**

K-Edge Subtraction Angiography with Synchrotron X-Rays, 525

State University of New York at Albany, Albany, NY**Walcek, C.J.**

Use of Cloud Observations and Mesoscale Meteorology Models to Evaluate and Improve Cloud Parameterizations, 818

Wang, W.-C.

Study of Regional Climate Changes, 771

State University of New York, Old Westbury, NY**Weinstein-Lloyd, J.B.**

Atmospheric Peroxides, 571

State University of New York at Stony Brook, Stony Brook, NY**Aller, R.C.**

Multiple Tracer Measurement of the Coupling Between Benthic C Fluxes and Bioturbation Activity During the Spring Bloom, 605

Cess, R.D.

Carbon Dioxide-Induced Climate Change, 772

Hameed, W.

Carbon Dioxide-Induced Climate Change, 772

Kirz, J.

X-Ray Micro-imaging by Diffractive Techniques, 444

State University of New York at Syracuse, Syracuse, NY**Hall, C.A.S.**Spatial and Temporal Patterns of Biotic Exchanges of CO₂ Between the Atmosphere and Tropical Landscapes and Their Role in the Global Carbon Balance, 851**Hahn, P.**

Construction of a Human Genome Library Composed of Multimegabase Acentric Chromosome Fragments, 385

Hozler, J.

Construction of a Human Genome Library
Composed of Multimegabase Acentric
Chromosome Fragments, 385

Lane, M.J.

Construction of a Human Genome Library
Composed of Multimegabase Acentric
Chromosome Fragments, 385

Syracuse University, Syracuse, NY**Siegel, D.I.**

Mechanisms Controlling the Production and
Transport of Methane, Carbon Dioxide, and
Dissolved Solutes Within a Large Boreal
Peat Basin, 819

Tennessee, University of, Knoxville, TN**Buonocore, E.**

Consortium to Develop Medical Uses of Nuclear
Magnetic Resonance Imaging, 527

Guckert, J.B.

Biochemical Markers for In Situ Microbial
Community Structure, 684

Phelps, T.J.

Biochemical Markers for In Situ Microbial
Community Structure, 684

Ringelberg, D.B.

Biochemical Markers for In Situ Microbial
Community Structure, 684

Sayler, G.S.

On-Line Monitoring of Aerobic Bioremediation
with Bioluminescent Reporter Microbes, 683

White, D.C.

Biochemical Markers for In Situ Microbial
Community Structure, 684
On-Line Monitoring of Aerobic Bioremediation
with Bioluminescent Reporter Microbes, 683

Tennessee, University of, Memphis, TN**Zeman, H.D.**

Intravenous Coronary Angiography Utilizing
K-Emission and Bremisstrahlung X Rays
Produced by Electron Bombardment, 526

**Tennessee Medical Center, University of,
Knoxville, TN****Kabalka, G.W.**

Boron in Nuclear Medicine: New Synthetic
Approaches to Positron Emission Tomography
and Single-Photon Emission Tomography
Agents, 528

Texas A&M University, College Station, TX**Bolch, W.E.**

Considerations of Beta and Electron Transport in
Internal Dose Calculations, 530

Marlow, W.H.

Atmospheric Aerosol Microphysics Formation,
Characterization, and Interaction, 572

North, G.R.

Signal and Noise in Global Warming Detection, 820

Poston, J.W.

Considerations of Beta and Electron Transport in
Internal Dose Calculations, 530

Walsh, I.D.

Optical Assessment of Large Marine Particles:
Development of an Imaging and Analysis System
for Quantifying Large Particle Distributions
and Fluxes, 607

Texas A&M University, Galveston, TX**Santschi, P.**

The Production of Colloids in the Benthic Boundary
Layer and Particle-Particle Interactions, 606

Texas, University of, Houston, TX**Siciliano, M.J.**

Sequence Tagged Sites for Human Chromosome 19
cDNAs, 395

**Texas, University of, M.D. Anderson Cancer Center,
Houston, TX****Jacques, S.L.**

Diagnostic and Therapeutic Applications of Diode
Lasers and Solid-State Lasers in Medicine, 529

**University of Texas, Medical Branch at Galveston,
Galveston, TX****Ullrich, R.L.**

Cellular and Molecular Mechanisms in Radiation
Carcinogenesis, 103

Thomas Jefferson University, Philadelphia, PA**Thakur, M.L.**

Evaluation of Biological Response Modifiers in the
Enhancement of Tumor Uptake of Tc-99m
Monoclonal Antibodies, 531

Tropix, Inc., Bedford, MA**Bronstein, I.**

Development of Chemiluminescence-Based DNA
Sequencing Kits and Systems, 396

Martin, C.S.

Chemiluminescent Multiprimed DNA
Sequencing, 397

Tufts-New England Medical Center, Boston, MA**Harling, O.K.**

A Clinical Trial of Neutron Capture Therapy for
Brain Tumors, 532

Zamenhof, R.G.

A Clinical Trial of Neutron Capture Therapy for Brain Tumors, 532

Tuskegee Institute, Tuskegee, AL

Blwas, P.K.

Effects of Enriched CO₂, Water, and Nutrient Stress on Sweet Potatoes: Towards the Development of a Universal Crop Simulation Model, 852

U.S. Department of Agriculture—Agricultural Research Service, Beltsville, MD

Acock, B.

Simulation Modeling of Crop Response to CO₂ Enrichment, 831

U.S. Department of Agriculture—Agricultural Research Service, Phoenix, AZ

Kimball, B.

Elevated CO₂: Modeling Cotton Response Interactions with Temperature on Photosynthesis, Insect Population Dynamics and Temperature Interactions and Long-term Effects on Trees, 833

U.S. Department of Agriculture—Agricultural Research Service, Gainesville, FL

Allen, L.H.

Assessment of Crop Response to Increased Atmospheric Carbon Dioxide: Rising CO₂ Effects on Rice, 832

U.S. Geological Survey, Denver, CO

Briggs, P.

Geohydrologic, Geologic, and Geochemical Processes Affecting Radon-222 in Groundwaters from Crystalline-Rock Aquifers, 685

Day, W.

Geohydrologic, Geologic, and Geochemical Processes Affecting Radon-222 in Groundwaters from Crystalline-Rock Aquifers, 685

Folger, P.

Geohydrologic, Geologic, and Geochemical Processes Affecting Radon-222 in Groundwaters from Crystalline-Rock Aquifers, 685

Frishman, D.

Geohydrologic, Geologic, and Geochemical Processes Affecting Radon-222 in Groundwaters from Crystalline-Rock Aquifers, 685

Poeter, E.

Geohydrologic, Geologic, and Geochemical Processes Affecting Radon-222 in Groundwaters from Crystalline-Rock Aquifers, 685

Wanty, R.

Geohydrologic, Geologic, and Geochemical Processes Affecting Radon-222 in Groundwaters from Crystalline-Rock Aquifers, 685

U.S. Geological Survey, Reston, VA

Gundersen, L.C.S.

An Investigation of the Geology and Geochemistry of Radon in Sheared and Fractured Rocks, 686

Reimer, G.M.

Gas Transport in Soils and Its Relation to Radon Availability: Identifying Regional Controls of Radon Availability, 687

University Corporation for Atmospheric Research, Boulder, CO

Schmel, D.

Climate System Modeling Program, 773

University of Medicine and Dentistry of New Jersey, Newark, NJ

Athwal, R.S.

Monochromosomal Hybrids for the Analysis of the Human Genome, 384

Utah, University of, Salt Lake City, UT

Ehleringer, J.R.

Water Use, Productivity, and Interactions Among Desert Plants: Vertical Integration Using Stable Isotope Ratios, 718

Giddings, J.C.

Field-Flow Fractionation of Chromosomes, 398

Gesteland, R.F.

Advanced Sequencing Technology, 399

Wells, R.

Advanced Sequencing Technology, 399

Vermont, University of, Burlington, VT

Albertini, R.J.

The Development of In Vitro Mutagenicity Testing Systems Using T-Lymphocytes, 104

Vermont College of Medicine, University of, Burlington, VT

Wallace, S.S.

An Immunological Approach to the Study of DNA Repair, 105

Virginia, University of, Charlottesville, VA

Herman, J.S.

Factors Affecting Transport of Bacterial Cells in Porous Media, 689

The Kinetics of Aromatic-Hydrocarbon

Biodegradation and Concomitant Geochemical Reactions Pertinent to Groundwater Systems, 688

Hornberger, G.M.

Factors Affecting Transport of Bacterial Cells in Porous Media, 689

- Mills, A.L.**
Factors Affecting Transport of Bacterial Cells in Porous Media, 689
- Wake Forest University Bowman Gray School of Medicine, Winston-Salem, NC**
- Wheeler, K.T.**
Direct Assays of Radiation-Induced DNA Base Lesions, 106
- Washington, University of, Seattle, WA**
- Hood, L.E.**
Megabase Sequencing of Human Immune Receptor Loci, 400
- Rosse, C.**
Modulation of Lymphopoiesis, 178
- Olson, M.V.**
Vertically Integrated Analysis of Human DNA, 401
- Washington Cancer Center, University of, Seattle, WA**
- Press, O.W.**
Improved Radioimmunotherapy of Hematologic Malignancies, 533
- Washington University School of Medicine, St. Louis, MO**
- Welch, M.J.**
Labeling of Receptor Ligands and Other Compounds with Halogen Radionuclides, 534
Preparation of Radiopharmaceuticals Labeled with Gallium and Indium, 535
- Westinghouse Savannah River Company, Aiken, SC**
- Addis, R.P.**
Atmospheric Transport of Contaminants, 562
- WGBH Educational Foundation, Boston, MA**
- Apsell, P.**
The Secret of Life, 402
- Chedd, G.**
The Secret of Life, 402
- Wisconsin, University of, Madison, WI**
- Anderson, J.R.**
An Experimental Regional Scale Climate Simulation Laboratory, 774
- Chait, B.**
High Speed DNA Sequence Analysis by Matrix-Assisted Laser Desorption Mass Spectrometry, 404
- DeLuca, P.M.**
Fast Neutron Dosimetry, 256
- Johnson, D.R.**
Modeling of Hydrologic and Transport Processes in Relation to Climate Change, 775
- Mead, D.**
Automation of the Front End of DNA Sequencing, 403
- Noordewier, M.O.**
Applying Machine Learning Techniques to DNA Sequencing Analysis, 406
- Porter, W.P.**
Physiological and Ecological Implications of Coupled Heat-and-Water-Transport Mechanisms of Endotherms and Vegetation, 719
- Shavlik, J.W.**
Applying Machine Learning Techniques to DNA Sequencing Analysis, 406
- Smith, L.M.**
Automation of the Front End of DNA Sequencing, 403
High Speed Automated DNA Sequencer, 405
High Speed DNA Sequence Analysis by Matrix-Assisted Laser Desorption Mass Spectrometry, 404
- Smith, W.L.**
Atmospheric Radiation Measurement Fourier Transform Spectrometer Data Analysis Tools, 821
- Stull, R.B.**
Parameterization of General Circulation Model Subgrid Nonprecipitating Cumulus and Stratocumulus Clouds Using Stochastic/Phenomenological Methods, 822
- Wisconsin Clinical Cancer Center, University of, Madison, WI**
- Clifton, K.H.**
Radiogenic Neoplasia in Thyroid and Mammary Clonogens, 107
- WNET/THIRTEEN, New York, NY**
- Moore, S.**
Medicine at the Crossroads, 407
- Page, G.**
Medicine at the Crossroads, 407
- Woods Hole Oceanographic Institution, Woods Hole, MA**
- Churchill, J.H.**
A Study of Sediment Motion and Bottom Boundary Layer Dynamics Over the Middle Atlantic Bight Shelf and Upper Slope, 612
- DeGrandpre, M.D.**
Fiber Optic Chemical Sensors for Characterizing the Carbon Cycle in Ocean Margin Regions, 609
- Druffel, E.R.M.**
Transformation Rates and Fate of Dissolved, Colloidal, and Particulate Forms of Organic Carbon in Ocean Margins, 610

Goyet, C.

CO₂ Measurements Along the World Ocean Circulation Experiment P-16 and 19 Sections in the South Pacific Ocean: A Joint Lamont-Dougherty Geological Observatory/Woods Hole Oceanographic Institution Program, 868

Repeta, D.J.

Characterization of Macromolecular Components of Particulate, Colloidal, and Dissolved Organic Matter at the Sediment-Water Interface: Implications for Organic Matter Degradation Versus Preservation During Early Diagenesis in Shelf Sediments, 611

Taylor, C.D.

Moored Instrument for Time-Series Studies of Primary Production and Other Microbial Rate Processes, 608

Woods Hole Research Center, Woods Hole, MA**Houghton, R.A.**

Spatial and Temporal Patterns of Biotic Exchange of CO₂ Between the Atmosphere and Tropical Landscapes and Their Role in the Global Carbon Balance, 853

Yale University, New Haven, CT**Turekian, K.K.**

The Determination of ²²²Rn Flux from Soils Based on ²¹⁰Pb and ²²⁶Ra Disequilibrium, 690

END

**DATE
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10 / 21 / 93