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Laboratory Directed Research & Development Program

**Annual Report to the Department of Energy
December 1996**

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Associate Director for Administration**

**BROOKHAVEN NATIONAL LABORATORY
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Acknowledgments

The Laboratory Directed Research and Development (LDRD) Program is directed by Nicholas P. Samios, Laboratory Director, and is administered by Henry C. Grahn, Associate Director for Administration (ADA). Until the end of Fiscal Year 1996, the LDRD Program was directed by Martin Blume, the former Deputy Director. Dr. Blume has returned to the research arena, and we thank him for his years of service to both the Laboratory and this Program. Preparation of the FY 1996 report was coordinated and edited by Gregory Ogeka and John Searing, Special Assistants to the ADA, who wish to thank Susan Cuevas, Regina Paquette, and D.J. Greco for their assistance in organizing, typing, and proofing the document. A special thank you is also extended to the Photography and Graphic Arts Group for their help in publishing. Of course, a very special acknowledgement is extended to all of the authors of the project annual reports and to their secretaries.

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Introduction

Background: Brookhaven National Laboratory (BNL) was established in 1947 on the site of the former Army Camp Upton. Brookhaven is a multidisciplinary laboratory that carries out basic and applied research in the physical, biomedical and environmental sciences, and in selected energy technologies. The Laboratory is managed by Associated Universities, Inc., under contract with the U. S. Department of Energy. BNL's annual budget has averaged about \$380 million, and its facilities are valued at over \$2.2 billion. There are about 3,300 employees, and another 4,000 guest scientists and students who come each year to use the Laboratory's facilities and work with the staff. BNL's Relativistic Heavy Ion Collider (RHIC), presently under construction, will be the world's foremost facility for nuclear physics research. RHIC will create the hot, dense plasma of quarks and gluons from which particles condensed after the "Big Bang" of the early universe.

Mission and Core Competencies: Brookhaven National Laboratory's mission is to support the basic Department of Energy (DOE) activities through its research and technology development, educational efforts, and industrial involvement. Brookhaven was founded as a laboratory which would provide specialized research facilities that could not be designed, built and operated at a university or industrial complex, and this still remains a basic mission of the Laboratory. Brookhaven National Laboratory has four core competencies.

Brookhaven's four core competencies: Research Facilities, Scientific Research, Technology Development, and Knowledge Transfer are not independent isolated competencies. They are interrelated in a complex manner.

MAJOR CORE COMPETENCIES

RESEARCH FACILITIES

Expertise to conceive, design, build and operate complex leading-edge, user-oriented research facilities in a safe and environmentally responsible manner.

SCIENTIFIC RESEARCH

Expertise to carry out basic and applied scientific research in long-term, high-risk programs. This is an essential capability needed to keep our research facilities at the leading edge. These programs lead to new insights and technological advances which provide the underlying scientific base for the DOE missions and generate long-term benefit to the nation.

TECHNOLOGY DEVELOPMENT

Expertise to develop advanced technologies that address national needs, support and strengthen the ability of DOE to carry out its missions, support other federal and state agencies, and enable industry to benefit from the multidisciplinary research and development at the Laboratory.

KNOWLEDGE TRANSFER

Expertise and mechanisms for disseminating scientific and technical knowledge to educate new generations of scientists and engineers to produce a technically trained workforce, to enhance scientific literacy of the general public, and to improve the competitiveness of U. S. industry.

Research Facilities and Scientific Research have a synergistic relationship. To maintain and constantly improve a research facility, and to keep it at the cutting edge, it is essential that the Laboratory have a significant research staff of excellent stature. The staff will drive the performance of the facility. Having the several complementary facilities at one location, such as the National Synchrotron Light Source and the High Flux Beam Reactor, allows a unique research capability, such as in material science and biological structure determination. The other two core competencies: Technology Development and Knowledge Transfer, bridges all of the research facilities and research programs.

Brookhaven's core competencies support and cut across the five central activities of the Department of Energy as defined in its Strategic Plan.

DOE Strategic Plan Activities	
SCI	Science and Technology
ENV	Environmental Quality
IND	Industrial Competitiveness
ENER	Energy Resources
SEC	National Security

BNL plays a major role in the Science and Technology, the Environmental Quality, the Industrial Competitiveness and the Energy Resources sectors, with a smaller, but special role in the National Security arena. In order to better see the connection between the various Brookhaven activities that form the core competencies and the Department of Energy Strategic Plan activities, each BNL activity/competency is followed with the letter code describing the match in the Table 1, "Major Activity Clusters."

Summary: New ideas and opportunities fostering the advancement of technology are occurring at an ever increasing rate. It, there-

fore, seems appropriate that a vehicle be available which fosters the development of new ideas and technologies, promotes the early exploration and exploitation of creative and innovative concepts, and develops new "fundable" R&D projects and programs if BNL is to carry out its primary mission and support the basic Department of Energy activities. At Brookhaven National Laboratory one such method is through its Laboratory Directed Research and Development Program. This discretionary research and development tool is critical in maintaining the scientific excellence and vitality of the Laboratory. Additionally, it is a means to stimulate the scientific community, fostering new science and technology ideas, which is the major factor in achieving and maintaining staff excellence and a means to address national needs within the overall mission of the DOE and BNL.

The Project Summaries with their accomplishments described in this report reflect the above. Aside from leading to new fundable or promising programs and producing especially noteworthy research, they have resulted in numerous publications in various professional and scientific journals and presentations at meetings and forums.

TABLE 1: MAJOR ACTIVITY CLUSTERS

LARGE RESEARCH FACILITIES

ALTERNATING GRADIENT SYNCHROTRON (SCI)

- Research in Particle and Nuclear Physics
- High-Intensity Frontier of Particle Physics
- World's Only High Energy Polarized Proton Source
- At Present, Nation's Only High Energy, Heavy Ion Synchrotron
- Over 800 Users

RELATIVISTIC HEAVY ION COLLIDER (under construction) (SCI)

- High-Temperature Frontier of Nuclear Matter
- Large and Unique High Energy Physics Potential (e.g. spin physics)
- 600 Users in First Round Experiments

HIGH FLUX BEAM REACTOR (SCI, ENER, ENV, IND)

- Instruments for Research in Condensed-Matter Physics, Biology, Chemistry, Applied Sciences and Industrial Applications
- 270 Users
- 21 Industrial Partners

NATIONAL SYNCHROTRON LIGHT SOURCE (SCI, ENV, ENER, IND)

- Two Storage Rings Providing Intense UV and X-ray Photon Sources
- Instruments for Research in Materials Science, Biology, Chemistry, Medical and Industrial Applications
- Over 3300 Users, Including 400 Industrial Users
- 79 Industrial Partners

BIOMEDICAL FACILITIES

PET-CYCLOTRON CENTER (SCI, IND)

- Medical Imaging for Basic Neuroscience and Substance Abuse, Radiotracer Synthesis

BROOKHAVEN LINEAR ISOTOPE PRODUCTION FACILITY (SCI, IND)

- Production of Isotopes for Medical Purposes
- Approximately 200 Isotopes Produced for Commercial and/or Research Use

MEDICAL RADIATION FACILITY (SCI, IND)

- Cancer Patient Treatment: 250 patients annually

BROOKHAVEN MEDICAL RESEARCH REACTOR (SCI, IND)

- Structural Biology, Molecular Masses
- Over 75 Users

PROTEIN DATA BANK (SCI, IND)

- World-Wide Repository for Three-Dimensional Structures of Biological Macromolecules

GENOME SEQUENCING CENTER (under development) (SCI, IND)

- Large-Scale DNA Sequencing

PROTON RADIATION THERAPY FACILITY (conceptual) (SCI, IND)

- Utilizes Existing 200 MeV Linac
- Will Consist of Horizontal and Vertical Beam Treatment Rooms
- Capability of 900 Cancer Patients Per Year

OTHER FACILITIES

TANDEM VAN DE GRAAFF FACILITY (SCI, SEC, ENV, ENER, IND)

- Microchip Radiation Testing Facility
- Film Irradiation Plant for Track Etching Filter Membranes
- 250 Users from 45 Institutions
- 53 Industrial Partners

ACCELERATOR TEST FACILITY (SCI, IND, SEC)

- Advanced Acceleration Concepts

10-MEV ELECTRON PULSE RADIOLYSIS FACILITY (commissioning) (SCI, ENER, ENV.)

- Study of Rapid Chemical Reactions: Catalysis, Energy Conversion and Storage

NUCLEAR DATA COMPILATION AND EVALUATION CENTER (SCI, SEC, IND)

- Nuclear Cross-Section and Structure Data
- 1100 Users

SCIENTIFIC RESEARCH

HIGH ENERGY PARTICLE AND NUCLEAR PHYSICS

(SCI)

- Beyond the Standard Model
 - Rare Kaon Decays
 - Muon Anomalous Magnetic Moment
 - Exotics and Glueball Spectroscopy
 - Neutrino Oscillation
 - Strange Matter
 - Solar Neutrinos
- Relativistic Heavy Ions
 - High-Temperature Nuclear Matter
 - Quark-Gluon Plasma

ADVANCED ACCELERATOR CONCEPTS

(SCI, IND, SEC)

- Short Wavelength Accelerating Structures
- Production of Coherent Radiation Free Electron Laser

MATERIALS SCIENCES

(SCI, ENER, IND, ENV)

- Materials Characterization with Neutron and X-ray Scattering, Magnetism and Superconductivity, Surface Studies, Corrosion, Adhesion, Catalysis, Metallic Alloys, Polymers

CHEMICAL SCIENCES

(SCI, ENER, IND, ENV)

- Molecular Dynamics, Reactive Transient Species, Thermal and Photo-Induced Charge Transfer, Structure and Reactivity

ENVIRONMENTAL SCIENCES

(SCI, ENV, IND)

- Global Change, Atmospheric Chemistry, Oceanography, Soil Chemistry, Cycling of Pollutants, Environmental Remediation

MEDICAL SCIENCE

(SCI, IND)

- Medical Imaging: PET, SPECT, MRI, Coronary Angiography
- Nuclear Medicine
- Radionuclides, Radiopharmaceuticals, Synthesis and Applications
- Advanced Cancer Therapies: Neutron Capture, Microbeam Radiation, Proton Radiation
- Mechanisms of Oncogenesis

MOLECULAR BIOLOGY AND BIOTECHNOLOGY

(SCI, IND)

- Genome Structure, Gene Expression
- DNA Damage and Repair
- Molecular Genetics
- Plant Science
- Bio-Structure Determination by X-ray and Neutron Scattering
- Enzyme Kinetics by Laue Crystallography
- Mass Measurements by Electron Microscopy

ADVANCED SCIENTIFIC COMPUTING AND SYSTEMS ANALYSIS

(SCI, IND, ENV, ENER)

- Risk Assessment
- Energy Modeling
- Groundwater Modeling

TECHNOLOGY DEVELOPMENT

PHYSICAL, CHEMICAL AND MATERIALS SCIENCE

(SCI, ENER, IND)

- State-of-the-Art Instrumentation and Devices for Precision Electronics, Optics and Microelectronics
- Superconducting Materials
- X-ray Lithography
- Micromachining
- Battery Technology
- Permanent Magnets
- Smart Polymers

ACCELERATOR TECHNOLOGY

(SCI, IND, SEC)

- High-Field, High-Quality Superconducting Magnets
- High-Power Radio Frequency Systems
- Ultrahigh Vacuum Systems
- Advanced Accelerator Designs
 - High-Gradient Acceleration
 - High-Beam Current Acceleration

ENVIRONMENTAL AND CONSERVATION TECHNOLOGIES

(SCI, ENV, ENER, IND, SEC)

- Environmental Remediation and Mitigation
- Energy-Efficiency Technologies
- Waste Treatment
- Disposal of Nuclear Materials
- Radiation Protection
- Infrastructure Modernization
- Transportation: Intelligent Vehicle Highway System, MAGLEV

MEDICAL TECHNOLOGIES

(SCI, IND)

- Biomedical Applications of Nuclear Technology
- Production of Radionuclides and Radiopharmaceuticals
- Development of Particle Radiation Therapies for Cancer
- Medical Imaging
- X-ray Microbeam Therapy

BIOTECHNOLOGY

(SEC, SCI, ENV, ENER)

- Neutron and Synchrotron X-ray Scattering
- Large-Scale Genome Sequencing
- High-Resolution Scanning and Cryo Electron Microscopy
- Cloning, Expressing and Engineering Genes
- Metal Cluster Compounds for Electron Microscope Labels
- Phage Displays for Probing Specific Interactions

SAFETY AND RISK ASSESSMENT

(SEC, SCI, ENV, ENER)

- Safeguards, Nonproliferation and Arms Control
- Safety Analysis of Complex Systems
- Probabilistic Risk Assessment

KNOWLEDGE TRANSFER

EDUCATING FUTURE GENERATIONS OF SCIENTISTS AND ENGINEERS

(SCI, ENV, IND, ENER, SEC)

- Lecturing, Conference Participation
- Visiting Scientist Program
- Accelerator Fellowship Program
- Postdoctoral Research Associates
- Engineering Intern Program
- Graduate Student Thesis Projects
- Adjunct Teaching Appointments at Local Colleges

- Office of Educational Program
 - Precollege and College Programs for Students and Teachers

EDUCATING THE GENERAL PUBLIC

(SCI, ENV, IND, ENER, SEC)

- Science Museum and Laboratory Tours (20,000 people/year)
- Speakers Bureau
- BNL Videos
- Laboratory Lectures for the Public
- Community Outreach Programs
- Information Storage and Transfer

TECHNOLOGY TRANSFER TO INDUSTRY

(SCI, ENV, IND, ENER, SEC)

- Industrial Users at the Research Facilities
- Consulting by Scientific Staff
- Technology Transfer Office
 - Patenting and Licensing Office
 - Technical Assistance for Industry
 - CRADAs
 - Visiting Scientist Program with Industry
 - Research Partnerships with Industry
 - Industry-Sponsored Proprietary Research and Development Long Island Research Institute (LIRI) (founding member)
 - Promotes Laboratory-Industry Interaction
 - ARPA-Funded BNL/LIRI Defense Conversion Project
 - NY State-Funded Biotechnology Initiative

INFORMATION TRANSFER

(SCI, ENV, IND, ENER, SEC)

- INFORM - Electronic Information Source
- Networking - "Information Superhighway"
- Technical and Scientific Publishing
- National Nuclear Data Center
- Protein Data Bank

Management Process

PROGRAM DESCRIPTION:

Introduction: The Department of Energy's (DOE) Laboratory Directed Research & Development (LDRD) Program at Brookhaven National Laboratory (BNL) was originally established as the "Exploratory Research Program" under the guidelines set forth in DOE Order 5000.1 in May 1984. From inception through September 1997, a period spanning thirteen fiscal years, the Laboratory has authorized \$30.2 million in Exploratory R&D, consisting of 178 separate projects.

BNL LDRD PROGRAM HISTORY 1985-1997

FISCAL YEAR	AUTH K\$	COSTED K\$	NO. REC'D	NEW STARTS
1985	1,842	1,819	39	13
1986	2,552	2,515	22	15
1987	1,451	1,443	29	8
1988	1,545	1,510	46	14
1989	2,676	2,666	42	21
1990	2,008	1,941	47	9
1991	1,353	1,321	23	14
1992	1,892	1,865	30	14
1993	2,073	2,006	35	14
1994	2,334	2,323	44	15
1995	2,486	2,478	46	13
1996	3,500	3,050	47	17
1997	4,500	—	71	11*
TOTALS	30,212	24,937	521	178

*Additional projects may be funded in FY 1997, pending the availability of funds.

Historical Perspective: Brookhaven National Laboratory was established in 1946.

Throughout its history, certain projects of an exploratory nature, sometimes referred to in the past as "seed money projects," were supported with overhead funding. In 1979, as a result of a Review Audit in that year, the seed money accounting procedures were formalized, and oversight by the then DOE Brookhaven Area Office Manager was first established. This seed money program operated at a variable level of funding, which averaged about 0.1 percent of the Laboratory's operating budget over the period 1979 to 1984.

In May 1984, the program was expanded. The expanded program embraced the new Exploratory R&D guidelines of DOE Order 5000.1. The new program, called the Exploratory Research Program, was put into effect for FY 1985 funding. The current Laboratory Directed Research & Development Program reflects the operating styles and many of the procedures of the earlier programs, which have evolved somewhat informally over the years. It also encompasses the requirements of the current DOE Order 5000.4A.

Goals and Objectives: The goals and objectives of BNL's LDRD Program can be inferred from the Program's stated purposes. These are to (1) encourage and support the development of new ideas and technology, (2) promote the early exploration and exploitation of creative and innovative concepts, and (3) develop new "fundable" R&D projects and programs. The emphasis is clearly articulated by BNL to be on supporting exploratory research "which could lead to new programs, projects, and directions" for the Laboratory.

General Characteristics of the LDRD Program: Projects or studies that are appropriate candidates for the Laboratory's LDRD Program include, but are not limited to, (1) projects, normally relatively small, in

the forefront areas of basic and applied science and technology for the primary purpose of enriching laboratory capabilities, (2) advanced study of new hypotheses, new concepts, or innovative approaches to scientific or technical problems, (3) experiments and analyses directed toward "proof of principle" or early determination of the utility of new scientific ideas, and (4) conception and preliminary technical analysis of experimental facilities or devices.

PROGRAM ADMINISTRATION:

Overall Coordination: Overall responsibility for coordination, oversight, and administration of BNL's LDRD Program resides with the Laboratory's Director. Until the end of this past fiscal year, the LDRD program was directed by the Deputy Director. The Office of the Associate Director for Administration assists in the administration of the program. This includes administering the program budget, establishment of project accounts, maintaining summary reports, and reports of Program activities to the DOE through the Brookhaven Group Manager.

Responsibility for the allocation of resources and the orchestration, review, and selection of proposals lies with a management-level group called the Laboratory Directed Research & Development Committee.

The Committee is made up of seven members. For Fiscal Year 1997, the Laboratory's Director is the chairperson of the Committee. The other members are the Associate and Assistant Directors of the Laboratory.

1996 LDRD PROGRAM COMMITTEE

Martin Blume	Chairperson and for Applied Programs
Mary S. Davis	Reactor, Safety & Security

Henry C. Grahn	Administration
Thomas Kirk	High Energy & Nuclear Physics
Denis B. McWhan	Basic Energy Sciences
Mark Sakitt	Planning & Policy
Richard B. Setlow	Life Sciences

Allocating Funds: There are two types of decisions to be made each year concerning the allocation of funds for the LDRD Program. These are (1) how much money should be budgeted overall for the Program; and (2) of this, how much, if any, should go to each competing project or proposal. Both of these decisions are made by high-level management.

Concerning the overall budget, for each upcoming fiscal year the Laboratory Director, in consultation with the Associate Director for Administration, develops an overall level of funding for the LDRD Program. The budget amount is then incorporated into the Laboratory's LDRD Plan which formally requests authorization from the DOE to expend funds for the LDRD Program up to this ceiling amount.

The majority of projects are authorized for funding at the start of the fiscal year. However, projects can be authorized throughout the fiscal year, as long as the approved ceiling for the LDRD Program is not exceeded.

The actual level of funding available for LDRD, however, may turn out to be much less than this ceiling. The actual level is determined during the course of the year and is affected by several considerations including: the specific merits of the various project proposals, as determined by Laboratory management and the members of the LDRD Program Committee; the overall financial health of the Laboratory; and a

number of budgetary tradeoffs between LDRD and other overhead expenses.

LDRD COSTS VS. TOTAL LABORATORY COSTS

operating \$ in millions

FISCAL YEAR	DOE FUNDS	WFO FUNDS	TOTAL FUNDS	LDRD FUNDS	% OF TOTAL
1985	153.0	40.4	193.1	1.82	0.9
1986	156.5	45.1	201.6	2.52	1.2
1987	161.7	45.6	207.3	1.44	0.7
1988	176.7	45.9	222.6	1.51	0.7
1989	193.6	46.7	240.3	2.67	1.1
1990	203.8	45.2	249.0	1.94	0.8
1991	220.9	50.3	271.2	1.32	0.5
1992	234.3	47.2	281.5	1.87	0.7
1993	231.4	47.3	278.7	2.01	0.7
1994	237.0	47.9	284.9	2.32	0.8
1995	243.0	53.7	296.7	2.48	0.8
1996	251.6	50.6	302.2	3.05	1.0

Concerning the allocation of resources to specific topic areas or to individual project proposals, such issues are addressed on a case-by-case basis by the LDRD Program Committee, once specific proposals have been received. The Committee meets periodically to review and recommend project proposals and to determine the amount of funding to be made available to the LDRD Program. The requirements of DOE Order 5000.4A are carefully considered during the selection process to ensure that proposals are consistent with DOE's criteria.

Request for Proposals: The availability of special funds for research under the LDRD Program is well publicized throughout the Laboratory. This is done using two methods, one occurring at yearly intervals, the other occurring irregularly. Each year in May a memo is sent by the Laboratory Director to all scientific staff issuing a "call for proposals." This memo is accompanied by a document entitled, "Guidelines and Procedures for Developing Proposals via the Laboratory

Directed Research and Development (LDRD) Program." The other method is by announcement in the Brookhaven Bulletin, the Laboratory's weekly newspaper; but the nature of the announcements varies, and they appear at irregular intervals. In some years the Bulletin prints an article that amounts to a separate call for proposals. In other years the Bulletin publishes articles on specific research projects which, in effect, help advertise the LDRD Program.

The "Guidelines and Procedures" document specifies the requirements necessary for participation in the program. It states the program's purpose, general characteristics, procedures for applying, and restrictions. An application for funding, that is, a project proposal, takes the form of a completed "Proposal Questionnaire." An application must be approved up the chain-of-command which includes the initiator's Department or Division Budget Administrator, the Department Chairperson or Division Head, and the cognizant Associate Director. Plans to ensure the satisfactory continuation of the principal investigator's regularly funded programs must also be approved. The applications are then forwarded to the Chairperson of the LDRD Program Committee for further review and consideration for funding.

The process which solicits and encourages the development of proposals has evolved into two modes of operation. Specifically, the ideas for proposal development may originate among the scientific staff in response to the general call for proposals. Alternatively, they may be initiated by top-level Laboratory management. Eventually, both follow the standard procedure for proposal approval up the chain-of-command to the same decision makers. The fact that all proposals must be approved up the chain-of-command permits BNL managers to consider all ideas together when designing the mix of projects for the LDRD Program.

An initiative from management typically takes the form of a general topic area or item of special interest. It is not a directive, nor is it included in the call for proposals, but the idea is communicated to a group of scientific staff, which is known to be in a position capable of pursuing and developing the idea in the form of a more formal proposal.

Proposal Review: Once a proposal is approved by the cognizant line managers, all proposals are forwarded to the Chairperson of the Committee who transmits a copy of all proposals received to the Committee for review. The Committee considers all proposals that have met certain minimum requirements pertaining to the Department's and BNL's LDRD policies.

Lead responsibility for the review of a proposal is then assigned to that member of the Committee who last approved it in the chain-of-command, that is, the member who oversees and directs the technical area from which the proposal originated. All members

have several weeks to review the proposal and prepare for the next Committee meeting. During this time, additional reviews, if desired, may be arranged.

Formal peer reviews, consisting of written comments by experts outside the normal lines of supervision, are not usually performed. The members of the Committee are considered to have sufficient technical knowledge so that peer reviews are seldom required.

At the next Committee meeting, the Committee member responsible for the review of the proposal presents the proposal to the other members of the Committee. This is done without the member necessarily becoming an advocate for the proposed project.

Selection Criteria: Before proposals can be considered by the Committee, they must be screened to ensure that they meet a set of minimum requirements concerning the Department's LDRD policies and the Laboratory's own guidelines.

Minimum requirements of each proposal are: (1) consistency with program purpose; (2) consistency with missions of BNL, DOE, and NRC; (3) approval by Department Chairperson and/or Division Head, and cognizant Associate Director; (4) assurance of satisfactory continuation of principal investigator's regularly funded programs; (5) modest size and limited duration; (6) will not substitute for, supplement, or extend funding for tasks normally funded by DOE, NRC, or other users of the Laboratory; (7) will not require the acquisition of permanent staff; (8) will not create a commitment of future multi-year funding to reach a useful stage of completion; and (9) will not fund construction line-item projects, facility maintenance, or general purpose capital equipment.

The selection criteria used to evaluate and

rank individual proposals are not formally stated or published. While the "Guidelines and Procedures" document clearly states that "awards will be made on a competitive basis," the factors or selection criteria to be considered in this competition are not listed. Nevertheless, selection is based on (1) scientific merit, (2) compliance with minimum requirements, (3) proposal cost as compared to the amount of available funding, (4) innovativeness, and (5) its potential for follow-on funding. The requirements of DOE Order 5000.4A are also carefully considered during the selection process to ensure that proposals are consistent with DOE criteria.

Project Approval: After all presentations are heard, the Committee attempts to arrive at a consensus concerning the highest priority proposals. Differences, if any, are resolved by the Chairperson. Also, a balance is struck between the prevailing financial needs of the Laboratory, which may vary over the course of the year, and the priorities of the projects considered. Some funding is held in reserve during the earlier meetings of the fiscal year so that funds remain available for proposals submitted at later dates. The funding amount requested in any one specific proposal may be changed or adjusted during the approval process. The Committee's recommendation is then submitted to the Director for his approval.

The Associate Director for Administration is then notified, so that a separate Laboratory overhead account can be established to budget and collect the costs for the project. Statistics on the number of projects approved, compared to those rejected, show an overall approval rate of about 36 percent for new starts. From inception of the program through September 1996, 521 project proposals were considered and 178 were approved. Eight scientific departments, the RHIC Project, and the Safety and Environmental Protection Division were represented in the FY 1996 LDRD Program.

Project Supervision: Supervision over the actual performance of LDRD projects is carried out in the same way as other research projects at the Laboratory. Each principal investigator is assigned to an organizational unit (Department, Division), which is supervised by a manager.

Each manager is responsible for seeing that the obligations of the principal investigator are satisfactorily fulfilled and that the research itself is carried out according to standard expectations of professionalism and scientific method. The manager is kept informed of the project's status, schedule, and progress.

FY 1996 FUNDING

BY ORGANIZATION

[] NO. OF PROJECTS

The manager ensures that the work is completed in a timely manner and that annual status reports are submitted to the Deputy Director. In addition, LDRD Program activity is reported to the DOE Brookhaven Group Manager, including copies of all funded proposals, a LDRD Program data base, and a project funding and schedule summary report.

Project Reporting: Routine documentation of each project funded under the LDRD Program consists of a file containing: (1) a copy of the written proposal; (2) all interim status reports; (3) notifications of changes in research direction, if any; and (4) reports on cost incurred. Also, a formal Annual Report on the LDRD Program is submitted to BNL management and the DOE, summarizing work progress, accomplishments, and project status on all projects.

Documentation for the overall Program consists of (1) various program history files, (2) a running list of all proposals with their acceptance/rejection status, (3) funding schedule and summary reports for all approved projects, (4) permanent records on cost accounting, and a data base containing information on each funded project (description, funding by fiscal year, status and accomplishments, follow-on funding, publications, etc.).

Some of the projects involve animals or humans. Those projects have received approval from the Laboratory's appropriate review committees. The projects which involve animals or humans are identified in this report as follows:

Note: This project involves animal vertebrates or human subjects.

This is noted on the summary sheet and also at the end of each report.

BROAD TECHNICAL AND SCIENTIFIC CATEGORIES:

Over the past several years, BNL has been categorizing its LDRD programs into six broad technical and scientific areas, including one miscellaneous area. The programs targeted for funding by BNL's LDRD Program fall into the following broad technical and scientific categories:

New Directions for Energy Technologies: In the course of basic research efforts, there are occasionally discoveries which hold promise for utilization in energy technologies. Such research is of significance, both for the Laboratory and for the DOE.

Environmental Science and Technology: BNL has a broad range of programs in environmental science. There are many important applications of our programs which we would like to exploit. These programs include atmospheric, oceanographic, and mathematical sciences, as well as efforts in environmental remediation. LDRD proposals in these areas, which move in new directions, are given priority as the Laboratory tries to make contributions to solutions of environmental problems.

Radiation Therapies and Imaging: Applications of the Laboratory's facilities to the treatment of cancer and in imaging of the human body for diagnostic purposes, including such techniques as functional MRI, microplaner x-ray therapy, neutron capture therapy and the use of other imaging techniques, are a significant part of the LDRD effort.

Genetic Studies: This area of research at the Laboratory has produced many new ideas and applications which are too important to remain undeveloped. LDRD funded projects in this area are varied in subject matter covering many bio-medical topics.

New Directions for the Development and Utilization of BNL Facilities: High priority is assigned to ideas for more efficient utilization and for new directions for our major facilities. Ideas for more useful sources of x-rays at the synchrotron light source, for the utilization of new electron sources in the chemical study of pulse radiolysis, and new

laser systems are all areas which are given priority for support.

Other Miscellaneous: Finally, the Program is open to significant and original ideas which do not necessarily fall within the bounds of the aforementioned priority areas. These usually involve small individual programs and projects that are judged to have high scientific/technical merit. Typically, materials development, electrochemical studies, advanced nuclear concepts and new bio-chemistry technologies fall into this category.

Brookhaven National Laboratory's FY 1996 LDRD Program covered the following Scientific and Technical Areas.

Programs/Projects	Funding \$000
New Directions for Energy Technologies	\$ 0
Environmental Science & Tech.	385
Radiation Therapies and Imaging	749
Genetic Studies	614
New Directions for the Development and Utilization of BNL Facilities	1,027
Other - Miscellaneous	<u>274</u>
TOTAL	\$ 3,049

SUCCESS INDICATORS:

Overall the BNL LDRD Program has been very successful. Some of the more common indicators/measures of success are: (1) the amount of follow-on funding received, (2) the number of proposals anticipating future funding, (3) the number of full-length papers published, (4) the number of post-doctoral students supported, (5) the number of scientists/guests hired, and (6) the number of copyrights, invention disclosures and patents applied for or granted.

Although it is difficult to maintain an accurate and timely database of these success measures for each project, a summary of the information reported is presented below. The difficulty in compiling data is the loss of contact with the principal investigators soon after the LDRD projects are concluded.

However, in an FY 1995 analysis, it was found that of the 54 projects which were funded during the period FY 1992 - 1994, 22 received follow-on funding, and 5 others were awaiting responses to proposals which have been submitted. The total amount of follow-on funding reported for the 22 projects involved was \$5.3M as compared to funding of these projects of \$2.5M. Other indicators reported during this period were:

Number of Projects with at Least 1 Full-Length Publication	33
Number of Post-Doctoral Students Supported	21
Number of Scientific Associates Hired	7
Number of Copyrights, Invention Disclosures, and Patents Applied For/Granted	12

In fact, only 10 of the 54 projects had none of the aforementioned success indicators to report.

It is estimated that cumulative follow-on funding reported for all projects funded from FY 1985 to FY 1994 is upwards of \$42M versus a total program authorization of \$19.7M during that period. This estimate is conservative since, as mentioned earlier, contact is not generally maintained with the principal investigator once the project has ended.

Summary of FY 1996 LDRD Program

In FY 1996, the BNL LDRD Program funded 31 projects, 17 of which were new starts, at a total cost of \$3,049,301. Following is a table which lists all of the FY 1996 funded projects and gives a history of funding for each by year.

Several of these projects have already experienced varying degrees of success as indicated in the individual Project Program Summaries which follow. A total of 16 informal publications (abstracts, presentations, BNL reports and workshop papers) were reported and an additional 33 formal (full length) papers were either published, are in press or being prepared for publication. The investigators on two projects (#95-04, #95-44) have filed for patents or disclosures. There were no new patents or disclosures filed in this fiscal year.

Seven of the projects reported that proposals/grants had either been funded or

were submitted for funding including one CRADA.

The complete summary of follow-on activities is as follows:

Follow-on Activity of LDRD Projects	
	Number of Projects
Informal Publications	16
Formal Papers	33
Grants/Proposals/Follow-on Funding	6
Patents/Disclosures Applied For	2
CRADA Application	1

In addition, numerous post doctoral candidates and guest scientists were supported or collaboratively involved in these projects.

In conclusion, a significant measure of success is already attributable to the FY 1996 LDRD Program in the short period of time involved. The Laboratory has experienced a significant scientific gain by these achievements.

Laboratory Directed Research and Development Fiscal Year 1996 - Summary of Projects

Project Number	Project Title	Dept.	Principal Investigator	Approved Budgets by Fiscal Year					Total Funding
				FY 1994	FY 1995	FY 1996	FY 1997 (estimated)	FY 1998 (estimated)	
94-06	Siberian Snake Prototype Development for RHIC	RHIC	M.A. Harrison	132,139	133,591	219,580	100,000	0	585,310
94-33	Low Mass, Low Cost Multiwire Proportional Chambers for Muon Systems of Collider Experiments	PHYS	V. Polychronakos	87,527	85,717	94,716	0	0	267,960
94-37*	Feasibility of SPECT in Imaging of F-18 FDG Accumulation in Tumors	MED	G.J. Wang	15,806	99,776	110,870	0	0	226,452
94-43	Visible Free-Electron Laser Oscillator Experiment	NSLS	I. Ben-Zvi	70,000	100,008	29,329	0	0	199,337
95-01	Study of Possible 2+2 TeV Muon-Muon Collider	PHYS	R.B. Palmer	0	149,580	200,185	240,000	0	589,765
95-03	Ultraviolet Free Electron Laser R&D	NSLS	E.D. Johnson	0	100,005	99,491	200,000	0	399,496
95-04	Precision Machining Using Hard X-rays	NSLS	E.D. Johnson	0	100,005	98,057	0	0	198,062
95-07*	New Directions in in-vivo Enzyme Mapping: Catechol-O-Methyltransferase	CHEM	Y.S. Ding	0	98,779	102,807	0	0	201,586
95-11	Development of Intense, Tunable 20-femtosecond Laser Systems	CHEM	E. Castner Jr.	0	66,937	64,605	0	0	131,542
95-13	Use of Extreme Thermophilic Bacterium Thermatoga Maritima as a Source of Ribosomal Components & Translation Factors for Structural Studies	BIO	F.W. Studier	0	92,696	96,402	0	0	189,098
95-15	Biochemical & Structural Studies of Chaperon Proteins from Thermotoga Maritima	BIO	J.M. Flanagan	0	75,762	98,776	0	0	174,538
95-33*	Low Dose Gamma Imaging Facility for in vivo Molecular Medicine	MED	R. Ma	0	109,736	110,070	5,000	0	224,806
95-40	Atmospheric Degradation of Halogenated Compounds	DAS	Z. Zhang	0	94,245	36,369	0	0	130,614
95-44	Extraction & Destruction of Hazardous & Toxic Chemical Pollutants during Soil/Sludge Remediation Using Innovative Technologies	S&EP	S. Chalasani	0	75,555	73,305	0	0	148,860
96-06*	Positron Emission Magnetic Resonance Imaging (PEMRI)	CHEM	C.S. Springer	0	0	100,208	170,000	0	270,208
96-10	Coherent Synchrotron Radiation Experiment	NSLS	J. Murphy	0	0	49,799		0	49,799
96-11	In-Vacuum Undulator (IVUN) for the NSLS X-ray Ring	NSLS	P.M. Stefan	0	0	100,118	100,000	0	200,118

* Project involves animal vertebrates or human subjects.

Laboratory Directed Research and Development Fiscal Year 1996 - Summary of Projects

Project Number	Project Title	Dept.	Principal Investigator	Approved Budgets by Fiscal Year					Total Funding
				FY 1994	FY 1995	FY 1996	FY 1997 (estimated)	FY 1998 (estimated)	
96-16	Spin Polarized Coincidence Spectroscopies	PHYS	P.D. Johnson	0	0	78,999	82,000	0	160,999
96-19	An Evaluation of the WSR-88D for the Remote Sensing of Cloud Properties	DAS	M.A. Miller	0	0	77,893	116,000	0	193,893
96-22	Studies of Nano-scale Structural Defects Using Advanced Electron Diffraction and Imaging Techniques	DAS	Y. Zhu	0	0	102,697	135,000	0	237,697
96-26	Research into New Database Methodology Based on the Object Protocol Model	BIO	E.E. Abola	0	0	14,394	100,000	95,000	209,394
96-27	Tailored Pulse UV/XUV Photon Source Development	CHEM	L.F. DiMauro	0	0	71,570	115,000	0	186,570
96-32	Methods for Detecting Activation of the DNA-Activated Protein Kinase, DNA-PK, in Human Tissue Culture Cells	BIO	C.W. Anderson	0	0	101,639	109,000	0	210,639
96-34	Enzymatic & Regulatory Interactions of a Single Protein with 3 Different Sites in Nucleic Acids	BIO	S.A. Lacks	0	0	111,076	119,000	0	230,076
96-37	Low Frequency Dynamics of Novel Materials	PHYS	M. Strongin	0	0	77,465	81,000	0	158,465
96-38*	BNCT for Leukemia Through Ex Vivo Purging of Bone Marrow	MED	J.A. Coderre	0	0	82,116	86,000	0	168,116
96-42	Designer Polymers for Permeable Ground Water Barrier Applications	DAT	D. Melamed	0	0	99,088		0	99,088
96-46	BNCT Treatment Planning Software Proposed Modifications	DAT	E.C. Selcow	0	0	157,773	195,000	0	352,773
96-48*	Comparison of Mutations in Fish Melanomas so as to Determine the Wavelengths Responsible for Human Melanoma	BIO	R.B. Setlow	0	0	103,050		0	103,050
96-49	Autecology of the Peconic Bay Brown Tide Organism, <i>Aureococcus anophagefferens</i>	DAS	J. LaRoche	0	0	98,405	104,000	0	202,405
96-50	Development and Demonstration of Accelerator-Based BNCT Capability	AGS	D. Raparia	0	0	188,449	412,000	200,000	800,449
				\$305,472	\$1,382,392	\$3,049,301	\$2,469,000	\$295,000	\$7,501,165

• Project involves animal vertebrates or human subjects.

LABORATORY DIRECTED RESEARCH AND DEVELOPMENT
1996 PROJECT PROGRAM SUMMARIES

Siberian Snake Prototype Development For RHIC

M.A. Harrison

94-06

PROJECT DESCRIPTION:

A helical dipole magnet is one in which the dipole field, rather than remaining vertical, rotates uniformly along the length of the magnet. Such magnets are required to do spin physics at RHIC. The parameters required include the following: $B \sim 4T$, aperture = 100 mm, low current operation ($<500A$) to minimize heat leak through many necessarily separated leads, and a pitch in the helix of approximately 180 degrees in one meter. There is no published record that such magnets have been built in the past; this is not surprising since they serve no useful purpose in normal accelerator or beam transport optics.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: The purpose of this R&D program is to demonstrate the feasibility of implementing polarized protons in the RHIC accelerator by constructing a prototype Siberian Snake module.

Approach: Design Principles: Various possible ways to build a helical magnet were considered without any particular method standing out as obviously superior. The usual rules of engagement for the building of superconducting magnets still apply: that high forces be contained, that superconductor motion (particularly stick/slip motion) be minimized, that energy be safely extracted from the magnet at quench, that the ends of the magnet be restrained, that cooling be

adequate for the operational conditions, etc. The design that is presently being developed borrows some concepts developed in the SSC and RHIC magnet programs, in particular the coils of the RHIC sextupole magnet and the assembly methods used for RHIC correctors. However, the critical question of how to build a spiral coil uses a new concept: grooves milled into a thick-walled aluminum cylinder to give a $\cos(\theta)$ current distribution when the grooves are filled with conductor. Unfortunately, this approach mandates that there will be considerable labor required in building model magnets because the many turns forming the coils will have to be wound by hand. The positive side of this approach is that models can be built without a large tooling expense. If this design goes into production, then a machine can be built to automatically wind the coils.

Technical Progress and Results: It was found that the superconductor wire being used in the RHIC corrector program could be used for the helical magnet design if it is wound into a 7-strand cable. This conductor, nearly one mm in diameter, would require 382A to produce a 4T field in the present design. By using this existing wire, the need to develop a new superconductor is circumvented. Using a cable in the magnet is preferable to using a single wire: if a break in a wire should occur, the magnet would very likely still operate. The required cable has been manufactured in sufficient quantity for several models of the present coil design. The required Kapton insulation was also wrapped onto the cable in the manufacturing operation.

As stated, this small diameter cable is hand-wound in an ordered pattern into slots milled into an aluminum cylinder. A piece of prepreg fiberglass cloth is placed between each layer of cables in the slots. When all the turns have been wound onto the cylinder, they are compacted with Kevlar wound under

tension onto the cylinder. And then the entire assembly is placed into an oven to cure at elevated temperature, thereby forming a series of current blocks around the cylinder in which each cable is firmly supported in a fiberglass/epoxy matrix. This design for supporting the cable turns is analogous to that developed for the wire turns in the RHIC sextupole magnet. The ends are then filled with a mineral-loaded epoxy to remove all voids, a technique used in the SSC program for adding strength and rigidity to coil ends.

Two of these cylinders, concentric with one another, are required to give the required field of 4T. These two cylinders will be mounted into an iron yoke using a support scheme as is being used for the RHIC corrector magnets. A helium containment shell is then welded in place around the yoke, serving also as the magnet support structure. From this point, the design is similar to that of the arc magnets for RHIC and all the same concepts and methods will be used as appropriate.

It is estimated that the helical magnet operating at 4.2K will have a margin in field of 30% above 4T, or 5.2T. The increased field has been achieved in this revised design by increasing the current turns in the coils, and by using a higher current in the outer coil relative to the inner coil to take advantage of the current capacity of the superconductor. Undesired harmonics were easily minimized in this design by adjusting the thickness of the walls between current blocks, a procedure analogous to adjusting coil wedges in a conventional magnet.

Status: A first coil was built and tested. It

was found that this coil quenched near short sample, with some modest training and some variation in the achieved quench currents. This result was quite encouraging and pointed the way to some changes in the assembly to enhance the quench performance.

An improved end design was used for the iterated model now being built. The new model will be a complete half length magnet in which the field rotates 180° over a length of 1.2m. Both coils for this model have been made and are awaiting test. Following the test of the individual coils, the complete magnet, including the yoke, will be assembled and tested.

Future Work: The test of the new half length model will complete the development phase of the helical magnets. The design that has been developed will be available as a choice in competition with an alternative design being built by an outside vendor. If the design developed in this program is chosen, then BNL staff will undertake to develop the tooling required and prepare for the production of the required magnets over the next several years.

FOLLOW-ON FUNDING:

The Japanese research institute at RIKEN has signed an agreement to fund the construction of helical magnets for RHIC.

LDRD FUNDING:

FY 1994	\$132,139
FY 1995	\$133,591
FY 1996	\$219,580
FY 1997 (est.)	\$100,000

Low mass, Low Cost, Multiwire Proportional Chambers for Muon Systems of Collider Experiments

V.A. Polychronakos

94-33

PROJECT DESCRIPTION:

Development of economical, mass production techniques of Multiwire Proportional Chambers (MWPC) appropriate for use with Muon Systems covering large solid angles in modern Collider Experiments. These chambers would utilize modern lightweight composite materials and provide all functions needed in a Muon System, i.e. precision momentum measurement, transverse coordinate, timing, and trigger.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: Multiwire Proportional Chambers have been in use for many years. Their spatial resolution is generally limited by the anode wire spacing and is of the order of one millimeter. This is inadequate for precision measurements of high momentum particles in planned or future High Energy Hadron Colliders where resolutions at the 100 micron level are needed.

Additionally, coverage of large solid angle requires chambers with the smallest possible dead space in the perimeter of the device. Ordinary proportional chambers usually feature massive frames in order to withstand the significant anode wire tension. The chambers under development in this project would provide all necessary functions required by a Muon System, i.e.:

- Precision coordinate for the momentum determination (<70 microns).
- The transverse coordinate with coarser resolution (1mm or coarser, as required by the particular application).
- Bunch crossing timing (3ns).
- Primitives for Level 1 trigger.

In addition they will be constructed using modern, lightweight composite materials resulting in high precision construction necessary for achieving spatial resolutions better than 100 microns while minimizing dead area in their perimeter.

Approach: The basis of our design is a low mass flat panel made of a parer (nomex) honeycomb core and copper-clad, 0.5 mm fiber epoxy facings forming the cathodes of the proportional chambers. These panels are approximately 2 cm thick and weigh about 1Kg per square meter. Three such panels, for example, would form a two layer chamber. One face in each gap is lithographically segmented into readout strips, typically, on a 5 mm pitch. Interpolation of the charge induced on these strips provides the precision momentum measurement coordinate. These panels are enclosed by suitable frames which provide the necessary features to complete the chambers. These are the 2.5 mm steps for the attachment of the anode wires, the printed circuit boards for the electrical connections, gas manifolds, a gas seal, bolt holes, etc. These frames are quite narrow (less than 5 cm for example) because the panels are stiff enough to withstand the wire tension of about 60 Kg/m. Even though the size of the frames has thus been dramatically reduced, they would still dominate both the weight of the detectors as well as their cost if ordinary materials such as fiberglass epoxy composites requiring extensive precision machining are used. Multiple Coulomb scattering is also the

dominant factor limiting the momentum resolution of such detectors. In this project we have been investigating alternate materials and fabrication methods for the construction of proportional chambers. The use of lightweight polymer concrete had been extensively investigated during the first year of this project. Low density casting materials with appropriate physical properties were identified and a series of samples were fabricated. Casting of the panels with such materials would drastically reduce the additional machining required, significantly reducing the fabrication cost. The initial cost of the casting forms, however, makes this technique suitable for very large experiments where such cost would represent a relatively small fraction of the total cost. During (FY 1995) other materials such as rohacell foams were also investigated and results from prototype work are summarized in last year's report. These materials would be appropriate for smaller experiments where the somewhat increased fabrication costs would still be below the required initial expenditure for the casting forms.

Technical Progress and Results: During FY 1996 we continued to pursue an alternative to polymer concrete approach appropriate for smaller experiments for which the initial cost of the polymer casting forms would not be justified. The fabrication of the nomex honeycomb panels using easily machinable, rigid polymethacrylimide foam was described in last year's progress report. During the past year a prototype detector was constructed using this technique. It consisted of three measuring planes of approximately one square meter each. The whole module weighed approximately 20 kg much of it due to the on-detector electronics. The prototype readout electronics were designed to test the behavior of the detector in a high rate environment expected to be encountered in most of the hadron collider experiments foreseen for the

next decade. Another new feature of this prototype detector was the use of the second cathode in each gas gap, segmented so that it can measure the transverse coordinate with a precision of about one centimeter. The advantage of this readout scheme compared to a readout of the anode wires to obtain the second coordinate is that the same electronics can be used for measuring both coordinates, thus reducing the overall cost of the detector. This prototype was tested last August-September at the M2 test beam of the Super Proton Synchrotron (SPS) of the European Organization for Nuclear Research (CERN). A low intensity muon beam was used to determine the spatial resolution of the device by comparing the measured position in one gap with the projected position of the track defined by the other two gaps. An intense Strontium source illuminating the chamber at the same time simulated the background rate of photons emitted by neutron capture that is expected in experiments at the European Large Hadron Collider (LHC). Figure 1 shows the measured spatial resolution as a function of background rate. A small degradation of the resolution can be seen with increased background rates. The performance degrades rapidly after about 5 kHz/cm^2 . It should be noted that the highest rate expected in the ATLAS Muon System, for example, is 0.7 kHz/cm^2 . Use of switched capacitor arrays for multiple sampling as opposed to a single sample used in the prototype readout is expected to improve the rate capability of this detector by at least a factor of two.

In parallel, and in collaboration with colleagues from Michigan State University, we investigated the feasibility of manufacturing light weight, high tensile strength conductive wire to be used for the anode wire planes. To this end we have considered the development of metal matrix composites consisting of fine carbon fibers embedded in a matrix of metal that could then

be shaped into a wire. Continuous carbon fibers with a 7 micron diameter are produced commercially by the precursor polyacrylonitrile (PAN) process. These fibers can be made with tensile strengths in the range 4.0 to 7.0 GPa and have a melting point ($>3000^{\circ}\text{C}$) much higher than most metals.

We considered PAN carbon fiber composites with a density of 1.8 gm/cm^3 and tensile strength $B=4.0\text{ GPa}$ yielding a specific strength $B/\rho=22\times 10^6\text{ cm}$. The resistivity of carbon fibers is much higher than the metals considered so that the electrical properties of the composite will be determined by the metal content. The resistance and specific strength of various metal matrix carbon fiber composites are shown in Figure 2 for metal fractions from 10% to 50% in 10% increments. A gold plated tungsten wire of 50 micron diameter, typically used in a chamber, has a resistance of 27 Ohm/m and $B/\rho=1.3\times 10^6\text{ cm}$. It can be seen that composites using a metal matrix of Al or Mg can have specific strengths an order of magnitude higher than that of a gold plated tungsten wire with the same ohmic resistance per unit length. The practical aspects of manufacturing such composites and verifying their predicted properties remains an open question which we will continue to pursue via other funding avenues.

PAPERS/JOURNALS/PUBLICATIONS:

G. Benze et al. "Position and Timing Resolution of the Interpolating Cathode Strip Chambers in a Test Beam", NIM A 357 (1995) 40-55

V. Grachev et al. "Double Track Resolution of Cathode Strip Chambers" NIM A 365 (1995) 576-581

Results from this work were also included in a paper with the title "Electromagnetic secondaries in the detection of high energy muons" published by the RD5 Collaboration (which includes our group) also in NIM (C Albarjar, et al., NIM A 364 (1995) 473).

FOLLOW-ON FUNDING:

Proportional chambers of this design have been accepted as the baseline technology covering the high eta region of the Muon System of the ATLAS experiment at the CERN Large Hadron Collider. BNL participates in this experiment and, pending approval of the whole project, DOE funding for further development of these chambers would be a realistic possibility.

LDRD FUNDING:

FY 1994	\$ 87,527
FY 1995	\$ 85,717
FY 1996	\$ 94,716

Figure 1.

Figure 2.

Feasibility of SPECT in Imaging of F-18 FDG Accumulation in Tumors

*Gene-Jack Wang and
Peter H.M. Kuan*

94-37

PROJECT DESCRIPTION:

To evaluate the feasibility of SPECT in imaging of ^{18}F FDG accumulation in tumors, we compare the sensitivity and specificity of PET and SPECT on ^{18}F FDG imaging of breast tumors. Patients who are suspected of having breast cancer following mammography will be recruited for this study. The patients will have a PET scan following injection of ^{18}F FDG. Images of chest and axillary region will be obtained using a SPECT system with high energy collimators following the PET scan.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: Prior to patient SPECT studies, systemic F-18 phantom studies are performed in order to document the detectable sizes (10 to 15 mm) and activity (μCi) at varying background conditions.

Approach: The present plan has been as follows:

1. Upon our completion of point source and phantom studied using ADAC dual-head SPECT equipped with 511 keV collimators at Stony Brook, we have begun to conduct similar investigations using the recently delivered Picker triple-head scanner at BNL. Satisfactory results will enable patient study to be initiated.

2. For image reconstruction, we will continue to use softwares provided by the equipment manufacturer. In addition, we will apply the following new methods which are expected to provide better quantitative distribution of radiotracer, thereby offering great potential for improving specificity and sensitivity in tumor detection.

- a) Multiwindow data acquisition and analysis of Dr.Z. Liang, Department of Radiology, SUNY Stony Brook, in addressing four basic areas: low-count density statistics, photon attenuation in patient, inclusion of scattered photons in data acquisition, and spatially variant detector resolution. The success of this method has been demonstrated in Tc-99m brain phantom studies.

- b) Monte Carlo calculations of F-18 511 keV SPECT images, toward identifying sources of image degradation and subsequent approach for image improvement, to be carried out with Dr. E. Selcow, Department of Advanced Technology under Project 96-46, Medical Physics Program Development.

Technical Progress and Results:

(1) Point Source Study of Uniformity Maps: For SPECT imaging, uniformity correction maps are to be generated and tested regularly to insure satisfactory camera condition. The image of a distant point source by rectangular NaI detector should be uniform. Without the uniformity correction map, the pattern of photomultiplier tubes will appear. With ADAC camera, we performed point source study of intrinsic maps generated by Tc-99m, Na-22 (511 keV), and Ge-68 (511 keV) to determine the suitable map for F-18 FDG SPECT QC work. Result of NEMA uniformity analysis, given in Table 1, leads to the following observations:

a. Ge-68 (pure 511 keV, 271 day half-life) is the QC source of choice for F-18 FDG studies.

b. F-18 FDG SPECT using Tc-99m generated map has a non-uniformity of 10% (4% or less recommended). Note that Tc-99m generated correction map as recommended by manufacturers was used in some clinical studies reported in the literature.

(2) The phantom studies: Results of F-18 brain and hot sphere phantom SPECT images with ADAC camera were given in BNL Report BNL-52351. Preliminary results with BNL Picker SPECT of the same hot sphere phantom is shown in Fig. 1, with 1.3 cm, 2 μ Ci/voxel sphere visible.

(3) Preparation for Patient Study at BNL Picker SPECT: We have recently received the delivery of special positioning pads for prone position breast imaging. We are initiating patient recruiting while completing additional phantom studies. Images from PET (F-18 FDG), SPECT (F-18 FDG), and MRI (Gd contrast) will be compared in sensitivity and specificity of tumor detection.

(4) Multi-window Data Acquisition: Picker has recently upgraded our software from version 6.8 to 7.2 and provided with an

unreleased PHA program to facilitate our multi-window imaging protocols. A spectrum of F-18 511 keV gamma ray with 4 windows is shown in Fig. 2. Point source raw data of photopeak window is shown in Fig. 3 for two images, at a distance of 10 cm and 30 cm from detector, respectively. Image degradation from finite collimator hexagonal holes and distance effect are clearly shown. These effects will be addressed and final image quality improved. Fig. 4 shows the 30 cm point source image upon initial data processing performed by Dr. J. Li of Dr. Z. Liang's Laboratory.

PAPERS/JOURNALS/PUBLICATIONS:

Kuan H.M., Wang G.-J., Volkow N.D., Schlyer D., Hamdan B., Oster Z.H. F-18 FDG SPECT: Point source and phantom studies. Medical Physics 23: 6 (1996) 1088.

LDRD FUNDING:

FY 1994	\$15,806
FY 1995	\$99,776
FY 1996	\$110,870

Note: This project involves animal vertebrates or human subjects.

Table 1. NEMA Uniformity Test of Point Source Generated Uniformity Maps

Integral Uniformity	Na-22 Point Source Tc-99m Generated Map	Na-22 Pt Na-22 Map	F-18 Pt Na-22 Map	Ge-88 Pt Tc-99m Map	Ge-88 Pt Ge-68 Map	F-18 Pt Ge-68 Map
Useful FOV	20%	3%	11%	13%	4.4%	4.4%
Central FOV	13%	1.5%	7%	9%	3.6%	4.0%

Fig. 1. BNL Picker SPECT phantom image of 5 hot spheres (Diameter 3.2, 2.5, 1.8, 1.6, 1.3 cm, 2 μ Ci/voxel) and a center line source (2 μ Ci/voxel) spaced in a circle of 11.5 cm diameter, inside a 20 cm diameter water-filled cylinder. Hot sphere of 1.3 cm diameter is visible.

Fig. 2. F-18 511 keV gamma spectrum with 4 window settings.

Fig. 3. F-18 point source image (raw data) from BNL Picker camera detector.

Fig. 4. The image of the point source at 30 cm from detector, shown in Fig. 3, after initial data processing.

Visible Free-Electron Laser Experiment

I. Ben-Zvi

94-43

PROJECT DESCRIPTION:

A Free-Electron Laser (FEL) oscillator is being studied at the short wavelength limit of the electron-beam-brightness. The wavelength is made short through the use of a very short-period undulator (micro-undulator). The 50 to 70 MeV electron beam of the BNL Accelerator Test Facility is being used in beam-line 3 of the ATF. Two types of undulators are available for the experiment: a pulsed electromagnet undulator made by MIT and a superferic undulator built at BNL. Both have a period of 8.8 mm. A successful demonstration of this short wavelength FEL oscillator will be an important step towards the realization of high power, tunable very short wavelength radiation sources in the VUV and X-rays. These sources may have important R&D applications in photochemistry, atomic and surface physics, biology and other sciences.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: In recent years, the emergence of research applications requiring intense, coherent, high brightness radiation sources beyond existing state of the art, has driven a wave of accelerator research and development. The NSLS has developed a proposal for the construction of a Deep Ultra-Violet FEL. An advisory panel chaired by Andrew Sessler of LBL recommended, among other things, the demonstration of the Visible FEL Oscillator Experiment. The motivation is the operation of a FEL near the emittance limit of the accelerator and, possibly,

extension to the near UV provided the beam brightness is as calculated.

Approach: The hardware of the Visible Free-Electron Laser experiment includes two 60 cm long microundulator with a period of 0.88 cm. One is a BNL built superconducting device and the other is an MIT built pulsed device. The superconducting undulator technology has been developed at the NSLS at BNL under a previous LDRD (91-22) project. We use a ferromagnetic yoke machined out of a solid block of low carbon steel. A superconducting NbTi coil is wound continuously along the yoke, with the winding direction alternating every half period. The magnetic field of this undulator is very uniform even for operation above saturation. The experiment is installed on beam line number 3 of the BNL Accelerator Test Facility (see figure). The FEL output will be at a wavelength of 500 nm at an electron beam energy of 50 MeV. The ability of the ATF to reach 70 MeV makes it possible to extend the operation of this FEL to the UV, about 250 nm. The FEL interaction and resonator design were studied in detail. An output power of 10 MW peak and a gain of about 25% are expected at the ATF beam parameters but with only 50 A peak current and a rms normalized emittance of 7π mm mrad.

Technical Progress and Results: During FY96 the ATF rf system has been upgraded to allow for a longer pulse train in the FEL operating mode. The upgrade required the change of both gun and linac klystrons and modifications to their modulators. The linac klystron has been replaced during an ATF shutdown in February and the gun system has been similarly upgraded in a July-August shutdown.

In addition to the rf system upgrade, the rf gun has been changed to an improved version that has already demonstrated a better beam

brightness. The photocathode laser injection path has also been improved to allow wavefront correction and eliminate various losses and optical damage problems.

In the meanwhile the experiment made progress in the use of the spontaneous emission of the undulator.

We developed a new method through which the properties of an electron beam at linac energies may be studied using the spontaneous emission of a microwiggler. The setup is simple and the measurement efficient. A simple set of scaling laws is derived to describe broadening of spontaneous emission in a narrow bandwidth radiation cone. The relations suggest that one can obtain beam divergence from a cone at large angle in a single shot measurement. A systematic series of experiments was performed with the MIT Microwiggler at the BNL ATF which demonstrated the response of the cone to changes in the beam quality. Estimates of divergence can be obtained from the measurements of the radiation cone.

We record the spatial profile of emissions into a Cerenkov cone selected by a 1 nm bandwidth interference filter. The radius of the cone can be controlled by varying the beam energy or filter central wavelength, while the cone width depends on the number of wiggler periods, and is further broadened by the beam energy spread, the beam divergence and the filter bandwidth. Systematic measurements of the emissions over a range in beam energy, energy spread, tuning parameters and wiggler field strength have been performed.

The experimental setup is shown in Figure 1. The electron beam passes through the microwiggler, the spontaneous emission is outcoupled and intercepted by the interference filter, and the remaining narrow bandwidth

constituent is recorded by the CCD camera.

Figure 1.

For the experiments described in this paper, a beam energy of 48 MeV and a train of 20 microbunches at 150-200 pC each was chosen. Nominal figures for energy spread and emittance were 0.5% full width and a few p mm-mrad, respectively.

At a fixed frequency, the contribution to the cone width scales differently with cone angle for the various broadening mechanisms. Simple expressions for the contributions of natural linewidth ($\sigma_{\text{cone,nat}}$), energy spread ($\sigma_{\text{cone},\gamma}$), and divergence ($\sigma_{\text{cone},x'}$) to the cone width in the wiggler plane are:

$$\sigma_{\text{cone,nat}} = \frac{1}{4N_w \gamma^2 \theta_{\text{cone}}} \left(1 + \frac{a_w^2}{2} \right) > 1 \quad (1)$$

$$\theta_{\text{cone}} \gg \frac{1}{\sqrt{N_w} \gamma}, \quad N_w \gg 1$$

$$\sigma_{\text{cone},\gamma} = \frac{\sigma_\gamma}{\gamma \gamma^2 \theta_{\text{cone}}} \left(1 + \frac{a_w^2}{2} \right) \quad (2)$$

$$\sigma_{\text{cone},x'} = \sigma_{x'} \quad (3)$$

The dependence of the S.E. cones was studied as a function of beam energy, interference filter incident angle, beam energy spread, wiggler field strength, misalignment, and various beam optics.

A scan in Figure 2a is particularly rich in information, and provided an opportunity to compare the scaling laws with experiment.

Figure 2. CCD Images showing dependence of S.E. cones on beam energy, energy spread and steering. The wiggler plane corresponds to the vertical axis. The color map represents emission intensity.

Figure 2a-c

The dependence of the S.E. cone on energy spread can be seen in Figure 2b and dependence on steering is demonstrated in Figure 2c. Clearly this diagnostic technique provides non-perturbative information on the electron beam divergence and energy spread. There is widespread interest in this type of diagnostic.

PAPERS/JOURNALS/PUBLICATIONS:

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G. Ingold, I. Ben-Zvi, L. Solomon and M. Woodle, Fabrication of a high-field, short-period superconducting undulator, Nuclear Instruments & Methods in Physics Research A375, 451 (1996),

Experiments in non-perturbative electron beam characterization with the MIT Microwiggler at the Accelerator Test Facility at BNL, X. Z. Qiu, P. Catravas, X.-J. Wang, M. Babzien, I. Ben-Zvi, J. Fang, W. Graves, H. A. Haus, Y. Liu, R. Malone, I. Mastovsky, Z. Segalov, J. Sheehan, R. Stoner, J. S. Wurtele to be published in Nucl. Instr. and Meth. in Phys. Res.

The work reported here is part of a Ph.D. thesis (in progress) of Ms. Palma Catravas, MIT.

LDRD FUNDING:

FY 1994	\$ 70,000
FY 1995	\$100,008
FY 1996	\$ 29,329

Study of Possible 2 + 2 TeV Muon-Muon Collider

*Robert B. Palmer and
Richard C. Fernow*

95-01

PROJECT DESCRIPTION:

The muon collider is being studied as a possible means for reaching the TeV energy regime at less cost than using hadron-hadron or electron-positron colliders. A conceptual design of a complete collider facility has been worked out, including all the necessary components starting from the muon production and ending with the collider detector.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: Muon colliders represent a possible approach to extending the high energy frontier of particle physics. Electron-positron colliders are believed to be constrained by energy loss due to beamstrahlung radiation and the expense of building two full energy linacs. The muon collider has negligible beamstrahlung and might be more economical, since it can make use of circular collider rings. A 2 + 2 TeV machine would be of moderate size (it would fit on the BNL site) and does not require the use of any exotic technologies.

However, many difficulties must be addressed. To fully understand the feasibility of this concept, it is important to simulate a complete facility from particle production to the intersection in the collider. Experiments should be performed to measure the efficiency of proposed pion production and collection ideas. The number of collected muons per incident proton on target is a crucial

parameter for determining the ultimate luminosity of the collider. Another crucial measurement is the efficiency of ionization cooling in reducing the emittance of the muon beam.

Approach: We have organized a design group, which meets weekly to discuss muon collider problems and concepts. We are collaborating in this work with groups at FNAL and LBL, as well as with interested individuals in other labs and universities. Work is presently concentrating on the design of a high energy 2 + 2 TeV collider and on a smaller 250 + 250 GeV collider.

Technical Progress and Results: A complete conceptual design for a 2 + 2 TeV collider has been determined, including a detailed parameter list. A Monte Carlo program has been written to simulate many aspects of the muon production and acceleration.

We have joined Experiment 910 at the AGS in order to measure the pion production spectrum in the appropriate kinematic regions. Data was taken this spring from a series of nuclear targets and over a range of incident proton momenta. Data analysis is currently underway.

A collection system based on a target inside a high field solenoid has been designed. An RF phase rotation system has been designed that reduces the momentum spread of the muon beam. The cooling system, which decreases the transverse and longitudinal phase space of the muon beam, is being studied with particle tracking and interaction codes. Work has begun on the design of rapid cycling synchrotrons for possible use in the accelerator rings. Work has continued on designing an isochronous, low-beta collider ring.

A physics group has continued work on:

(1) physics processes that can be measured at a muon collider, (2) the expected backgrounds at the intersection region due primarily to muon decays, and (3) the design of a generic detector.

A major presentation of the muon collider concept was made to the high energy physics community at the 1996 Snowmass Workshop. The muon collider work was summarized in a 480 page feasibility study.

PAPERS/JOURNALS/PUBLICATIONS:

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R.B. Palmer et al, Progress on the design of a high luminosity muon-muon collider, BNL report 63245, 1996.

A. Garren et al, Design of the muon collider

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R. Palmer et al, Muon collider design, BNL report 62949, 1996.

J.C. Gallardo & R.B. Palmer, Final focus system for a muon collider: a test model, BNL report 62759, 1996.

R.B. Palmer et al, Muon Colliders, BNL report 62740, 1996.

R.C. Fernow et al, Possible demonstration of ionization cooling using absorbers in a solenoidal field, BNL report 62583, 1995.

LDRD FUNDING:

FY 1995	\$149,580
FY 1996	\$200,185
FY 1997 (est.)	\$240,000

Ultra-violet

Free Electron Laser R&D

Erik D. Johnson

95-03

Ilan Ben-Zvi

Richard Heese

Sam Krinsky and

Li-Hua Yu

PROJECT DESCRIPTION:

The NSLS has identified short wavelength Free Electron Lasers as a possible new source for its synchrotron radiation research community. Considerable research and development work has already taken place at BNL on many of the component technologies necessary to prototype such a device. Key among these elements is an accelerator designed to produce short pulses of electrons with low emittance and high peak current. Several types of synchrotron radiation sources can utilize such a machine, including a coherent transition radiation source, a coherent synchrotron radiation source, as well as a short wavelength Free Electron Laser. This suite of experiments is now known collectively as the Source Development Laboratory (SDL). The SDL utilizes equipment recovered from various terminated projects notably the ARPA 210 MeV linac, and the 10 meter long NISUS undulator from the Army SSDC. The goal of this LDRD project is to support the integration of these existing technologies into an accelerator designed to prototype an UV-FEL.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: A full CDR has been developed for an ultra-violet free electron laser designed to operate into the deep UV. The so-called

DUV-FEL proposal cost estimate is roughly \$30M for its full implementation. Much of the pre-construction R&D it would require can be accomplished on existing or loaned equipment, running at reduced repetition rate and tuning capability. This experiment, called the ultra-violet project free electron laser (UP-FEL) seeks to perform a reduction to practice in a proof of principle experiment. Many of the existing components must be adapted or improved from their present form. This LDRD project covers some of the R&D required to execute the proof of principle experiment for the FEL

Approach: The DUV-FEL Conceptual Design Report forms the basis for the design of the Source Development Lab accelerator. It requires the production and delivery of a very bright electron beam to an amplifier, in this case comprised initially of the NISUS undulator. To generate the electron beam, the 'Gun III' design developed in an Accelerator Test Facility (ATF) collaboration has been adopted. To be confident that the accelerator can preserve the bright beam produced by the gun, and that compression can be achieved without emittance dilution, extensive simulations have been undertaken in collaborations with other laboratories, and through R&D subcontracts.

Technical Progress and Results: The 'Gun III' collaboration was established prior to the funding of this LDRD, so much of the conceptual design work had already been performed. The gun is basically a simplified version of the well established ATF RF photocathode electron gun. The SDL project benefits from this previous work, and has contributed to supporting the development of the first prototype gun, which was fabricated during FY 96. The gun is shown in figure 1.

Simulations of the gun performance, initial cold testing, and tuning have previously

been reported [1]. The construction of the integrated system, including emittance compensation solenoid was completed, and commissioning is now well underway [2] at the BNL ATF. The prototype system is shown in figure 2. Based on preliminary data from this commissioning, only minor modifications to the design will be required for implementation at the SDL.

Figure 1 The first operational copy of the Gun III built in a BNL/SLAC/UCLA collaboration.

Figure 2 Integrated Injector system.

Similar systems are also being fabricated for the SLAC electron gun test stand, and the UCLA physics department.

The SDL project similarly benefits from prior work conducted by the BNL Chemistry department for its Center for Radiation Chemistry Research (CRCR) facility in specifying a gun laser system. An electron gun similar to that for the SDL is employed in the CRCR which required the specification of a gun laser system. After considerable investigation of alternatives, a Spectra Physics Titanium:Sapphire (Ti:Sap) laser was selected. To maintain some commonality between the facilities, the same basic laser system was specified for the SDL. For the CRCR, this laser provides the opportunity for multi-color experiments, while at the SDL, radiation from the gun laser can be split off for seeding the FEL, resulting in very low timing jitter. Installation and commissioning of this system is anticipated for early 1997.

During FY 96 considerable effort was also invested in setting up a control system for the SDL which is based on the same hardware as the NSLS accelerator plant. The commonality of hardware and software (once the low level interface development is complete) has several benefits. Software modification and maintenance should be comparatively straight forward. New features developed for the NSLS control system should be directly compatible with the SDL control system. Perhaps most important is that staff members familiar with the NSLS control system should find it comparatively easy to operate the SDL accelerator. The programming segment of this activity has been largely completed, and awaits the installation of the linac for further development.

An issue of recent concern has been the possibility of emittance "blow up" in bending magnets, such as those designed for our bunch

compressor, due to centrifugal space charge forces and coherent synchrotron radiation emission. From the standpoint of the FEL, any dilution of emittance arising from these effects in the pulse compressor could negate any benefit to be derived from the shorter pulses and higher peak current it would produce. To address these questions we have undertaken a program of extensive simulation and modeling of the accelerator. These results have been presented at international meetings [3,4].

We believe that our current machine design properly accounts for these effects, and provides us with a basis for understanding the anticipated operating envelope of the accelerator. In the coming fiscal year, we hope to proceed with the development of the experiment at BNL. We also anticipate an expansion of our collaborations within BNL, and with other institutions, to develop a technological base for addressing the important questions relating to the construction and operation of a single pass ultra-violet free electron laser.

PAPERS/JOURNALS/PUBLICATIONS:

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1.6-cell photocathode RF gun", by D.T. Palmer, R.H. Miller, H. Winick, X.J. Wang, K. Batchelor, M.H. Woodle, I. Ben-Zvi, **SPIE Proceedings 2522**, p 514, (10-14 July 1995 San Diego, CA)

[2] "Commissioning Results of the Next Generation Photoinjector," D.T. Palmer, X.-J. Wang, R.H. Miller, I. Ben-Zvi, C. Pellegrini, J. Sheehan, J. Skaritka, H. Winick, M. Woodle and V. Yakimenko, Proc. 7th Advanced Accelerator Concepts Workshop, Lake Tahoe, Oct. 13-18, 1996

[3] "The BNL Source Development Laboratory", I. Ben-Zvi, E. Blum, W.S. Graves, R.N. Heese, E.D. Johnson, S. Krinsky, J.B. Murphy, L.-H. Yu, Presented at the FEL96 Conference, Rome Italy, August 26-31 1996. To appear in Nucl. Instrum. & Methods.

[4] "The Source Development Lab Linac at BNL", W.S. Graves, E.D. Johnson, T.O. Raubenheimer, Proc. Linac-96 Conference, Geneva Switzerland, August 1996.

LDRD FUNDING:

FY 1995	\$100,045
FY 1996	\$ 99,491
FY 1997 (est.)	\$200,000

Precision Machining using Hard X-rays

*Erik D. Johnson and
D. Peter Siddons*

95-04

PROJECT DESCRIPTION:

Previous work under this LDRD has shown that hard x-rays, such as those available from the NSLS X-27B beamline used for this research, can indeed extend the lithographic processing of resist materials to the scale of several centimeters while maintaining precision at the level of microns. We have implemented techniques of coupled scanning of substrate and mask to produce fully figured three-dimensional structures in plastic. This project is a systematic study of these techniques and the processing parameters required to operate with confidence in this high aspect ratio regime. Apart from the basic research interest of understanding the materials science aspects of this problem, demonstrations of process efficacy and reductions to practice of this technology should provide potent motivation for its commercialization.

Indeed, the early results of this LDRD program lead to the filing of a patent which details the fundamental principles of the process, and possible applications of hard x-ray lithographic manufacturing [1]. The interest expressed from industry in this technology [2] has in fact lead us to establish a new beamline (X-14B) as a 'prototype production research' capability.

The DOE has funded this new work through the Sustainable Technology Initiative, hence we feel this LDRD project has 'graduated' into a real program. It is our hope, that from this promising start, we can

maintain a stable line of research in this area, and promote a growth in user base for the NSLS.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: The idea of using the lithographic techniques developed by the microelectronics industry to fabricate micromechanical components began to take shape in the mid-80's. By 1988 a group in Germany was sufficiently convinced of its future importance to float a commercial enterprise to capitalize on the techniques developed by the research group based at the Karlsruhe Nuclear Research Center working on the BESSY storage ring in Berlin. At roughly the same time a group headed by Prof. H. Guckel at the University of Wisconsin at Madison began to develop their own techniques in this area, using the ALADDIN storage ring at Madison. Almost all of the programs existing or proposed make use of soft x-rays to fabricate tiny structures which are essentially 2-dimensional.

Our work under this LDRD has followed two main paths. The first is directed at developing methods for the very precise manufacture of macroscopic, three-dimensional structures using hard x-rays in a lithographic process, and was the main focus of our efforts in FY 95. We demonstrated that, at least on a prototype basis, complex 3-dimensional objects can be machined with sub-micron precision. The second thrust of this research is to seek optimal solutions for the production of high aspect ratio structures in quantity, which would be economically attractive for commercial applications. We have focused our attention in this direction during FY 96, and feel that the characteristics of the hard x-ray based technology are more than amenable to several strategies to achieve this goal.

Approach: Early in this work, we made some test objects which showed that fully figured plastic masters could be made. To proceed to the manufacture of 'real devices' one must be able to transfer the mask pattern to the plastic while holding dimensional tolerances. This can not be done without a suitable masks and measurement tools. For the measurements, we employ an electron microscope, and an optical microscope with an encoded translation stage to make comparisons between the mask and exposed parts. We use these tools to systematically investigate the effect of varying the exposure and development conditions on the quality of the finished plastic parts.

For masks, we have continued to use silicon supported gold patterns fabricated by conventional LIGA methods, and a variety of 'kinematic' masks. As part of this work, we have developed a controllable aperture system to be used for 'writing' objects which can be represented by the superposition of rectangular shapes.

We have limited our choice of resist material to polymethyl-methacrylate (PMMA) as it is readily available and well studied with regard to its properties as a thin film photo-resist. It is a 'known' quantity within the micro-electronics community, and therefore we reasoned, would be more readily adopted as part of a new technology. We have also selected 2-methyl-4-pentanone, (methyl-isobutyl-ketone or MIBK) as our developer for similar reasons. Although other, more complex, developers are often used in LIGA processing, our work has shown that the MIBK is actually superior for the type of structures we have made thus far.

In pursuing this research, we are making both tolerance test structures, for studying processing parameters, and fabricating structures directly in plastic for selected

applications. This is done to gain an understanding not only of the resist and processing properties, but to maintain an awareness of manufacturability issues throughout the course of the research.

Technical Progress and Results: The following photographs provide some idea of the potential for these techniques. The first obvious step is to fabricate structures not unlike existing LIGA technology, in as much as they are essentially figured only in two dimensions, as shown in figure 1. The first obvious difference as contrasted with conventional lithography is the thickness of the parts. We have exposed samples many millimeters thick, including producing a square hole 1mm across, but over 100 mm deep. Figure 1 gives a qualitative feel for the finish provided by hard x-ray lithographic exposure (the side walls) as compared with conventional diamond machining (the front face of the PMMA). It also exhibits faithful reproduction of the mask features (crisp corners and defects) and no observable runout from the front of the resist to the wafer surface.

Figure 1 Lettering in 1 mm thick PMMA sheet. At right is the point of a tailors pin. Note the smooth side walls as compared to the conventionally diamond machined surface of the acrylic sheet.

This example demonstrates many of the processing advantages realized by the use of hard x-rays. For example, the mask was a 50 μ m thick gold pattern on a standard silicon wafer. As a mask, this object is far more robust than any used for conventional soft x-ray lithography. The shorter wavelength also means that diffraction blurring is negligible.

In the work described in the FY 95 progress report, we emphasized developments that allow for the fabrication of fully figured three dimensional objects. In particular, we have manufactured parts which are essentially solids of rotation including pieces with reentrant volumes [3]. While this aspect of the research has generated significant interest, it appears that at the bulk of applications presently at hand involve the rapid production of high aspect ratio structures over large areas.

An example of this type of application is a series of long channels in 1mm PMMA sheet, as prototypes for high density Gel-electrophoresis columns [4]. A sample array is shown in figure 2, where we have manu-

Figure 2 125 μ m wide tracks in 1 mm thick PMMA sheet. Pitch is 500 μ m.

factured a series of 50 or more channels through 1mm thick PMMA sheet, which are 40 mm long by 125 ± 3 μ m wide, with a 500 μ m spacing between channels. While the compactness of this array is impressive, the more important feature is the smoothness of the sidewalls, which would be difficult to achieve by conventional machining methods. The finish of these surfaces is important to minimize wall drag and elution spread in the macromolecules being driven through the channel. For a functional device, the technique will need to be extended to allow fabrication of channels up to 500 mm long. To scale up to this length, we have undertaken the development of a long throw, high speed scanner.

The prototype scanner has a stroke of up to 25" [635 mm] and can run at rates as high as 10"/second [254 mm/s]. The rate and position are determined by analog signals and the system has position feedback provided by an LVDT. This stabilizes the placement of the scanner stage to better than 10 μ m absolute position. The scanner is controlled by a PC running a Labview system which has been written to allow several modes of operation. In addition to fixing the scan stage parameters, the exposure parameters can be selected, including the total exposure, and the exposure rate. We have found that this latter parameter, which is not often included in the description of the work of others in the field, significantly effects the way in which an exposed sample develops.

The prototype scanner was built for use on our existing X-27B beamline, but it has proven sufficiently successful that it will be the basis for the design of the scanner to be installed in our prototype production beamline, X-14B.

On X-27B, we have continued with other aspects of our process development work.

One element which can be a limiting factor in bringing a device from concept to exposed plastic part can be the fabrication of a mask. In situations where suitable kinematic (machined) masks are inappropriate, due to size or tolerance for example, we must use lithographically produced masks. These devices are themselves soft x-ray LIGA manufactured objects which can take a significant time to obtain. To date, the test masks we have used are 50 μm gold absorbers electrodeposited on silicon wafers typically 200 μm in thickness. These masks have been fabricated for us by Professor Guckel's group at the University of Wisconsin, and require a significant effort on their part.

To eliminate the intermediate steps, we have started to investigate a method for the 'direct writing' of masks using controlled apertures and resist manipulation stages. The part shown in figure 2 was actually produced using a prototype vertical aperture. This device was incorporated in the design of the two axis aperture system shown in figure 3.

This device consists of a pair of molybdenum rods mounted horizontally just off the center of rotation of a drum affixed to a sine arm mechanism. By rotating the drum, the projected spacing between the rods can be changed in a controlled manner. The rods are mounted in such a way as to minimize the effect of heating on the apparent opening of the aperture. The pusher for the sine arm has an absolute linear encoder used in a feedback loop to set and maintain the position of the sine arm. The flexural pivots used to hold the drum ensure that the center of rotation of the drum is fixed. The horizontal masking is achieved using two independent stages which drive molybdenum rods mounted on bell cranks. These rods can be positioned anywhere in the 40 mm field, so within that field, a horizontal aperture of any size and

placement can be obtained. The bell crank design was selected to provide the greatest immunity to beam heating induced aperture size changes. It also minimizes the horizontal space occupied by the assembly. By mounting the sample on a rotary stage resting on a separate lift platform, areas of any size and orientation can be exposed (within a 40 mm field).

Figure 3 Photograph of x-y writing apertures. The vertical aperture drum is at the right of the photo. The horizontal masks are to the left.

With this device, we hope to be able to write structures directly for the manufacture of masks, and possibly for 'one-off' devices in plastic. In addition, it should be an invaluable aid in our continuing investigation of the influence of exposure patterns and proximity on device fabricability and processing.

PAPERS/JOURNALS/PUBLICATIONS:

[1] US Patent Application 'Method and Apparatus for Micromachining using Hard X-rays', D.P. Siddons, E.D. Johnson, H. Guckel, J.L. Klein co-inventors. 21 Figures, 70 Claims, Assigned jointly to BNL, and WARF (Wisconsin Alumni Research Foundation)

[2] 'Hard X-ray Precision Fabrication

Workshop', D.P. Siddons, E.D. Johnson, Synchrotron Radiation News, Vol. 9 No. 5 (1996) p9.

[3] 'Precision Machining with Hard X-rays: Experiments at the NSLS', E.D. Johnson, J.C. Milne, D.P. Siddons, H. Guckel, J.L. Klein, Synchrotron Radiation News, Vol. 9 No. 4 (1996) p10.

[4] BNL CRADA BNL-C-95-07 'Instrumentation for High Throughput DNA Sequencing', J.C. Sutherland PI.

FOLLOW-ON FUNDING:

Based in part on the success of the work

supported by this LDRD project, a new FWP line has been established to support continuing research within the NSLS. The present program is directed to the development of a prototype production station at X-14B. Once established, it is hoped that this line will be used for proving the viability of hard x-ray microfabrication in the commercial arena, and encouraging the growth of a new segment of the user community for the NSLS.

LDRD FUNDING:

FY 1995	\$100,005
FY 1996	\$ 98,057

New Directions in *in vivo* Enzyme Mapping: Catechol- O-Methyltransferase

Yu-Shin Ding

95-07

PROJECT DESCRIPTION:

Catechol-O-Methyltransferase (COMT; EC 2.1.1.6) regulates the concentration of important catecholamine neurotransmitters such as dopamine. It is also a new molecular target in the development of drugs to treat Parkinson's disease (PD). Though the major function of COMT was described first in the 1950's and its structure was recently elucidated, there is limited information on its regional distribution or functional significance in the living body or of changes in its activity occurring in diseases. With the recent development of selective and potent COMT inhibitors, we now have the opportunity to probe the distribution of COMT *in vivo*.

TECHNICAL PROGRESS AND RESULTS - Fiscal Years 1995-1996

Purpose: The goal of this proposal is to develop and validate the methodology for mapping COMT activity *in vivo* using PET. Specific aims include:

1. Synthesis and evaluation of the first positron emitter labeled COMT inhibitor as a radioligand for mapping COMT *in vivo*.
2. Exploration of the potential of the new COMT radioligand as a tool in pharmaceutical development and for monitoring COMT inhibitor therapy for Parkinson's disease.

Approach: In order to examine the distribution and functional activity of COMT

in the living system, Ro41-0960 (2'-fluoro-3,4-dihydroxy-5-nitrobenzophenone), a fluorine containing, potent and selective COMT inhibitor, was chosen for labeling. Enzyme kinetic studies indicated a reversible tight binding type interaction between COMT and Ro41-0960. These characteristics generally fit a major requirement for mapping COMT *in vivo*; namely, that the binding of the labeled inhibitor to the enzyme should be tight enough to allow of visualization of the enzyme-substrate complex. Additionally, reports that Ro41-0960 crosses the blood-brain barrier (BBB) inhibiting brain COMT activity supported the development of a rapid synthetic route to [^{18}F]Ro41-0960 as a radiotracer for central and peripheral COMT distribution.

Technical Progress and Results: Summary of Technical Progress and Results for Fiscal Year 1995: Over the past year, we have completed the first synthesis of an F-18 labeled ($t_{1/2} = 110$ min) COMT inhibitor ([^{18}F]Ro41-0960) and have initiated PET studies. Preliminary studies of COMT have been reported in LDRD Program-Annual Report FY 1995 and are summarized as follows: (1) we can synthesize [^{18}F]Ro41-0960 in sufficient yield for PET studies; (2) [^{18}F]Ro41-0960 has low cerebral bioavailability, in contrast, to the many claims of its central activity in the literature; (3) a significant low plasma free fraction and high erythroplasmatic ratio suggests that high degree binding to plasma protein rather than binding to erythrocyte may explain, at least in part, the exclusion of [^{18}F]Ro41-0960 from the brain; (4) tracer uptake is highest in kidney and liver which is consistent with high levels of COMT in these peripheral organs; (5) it labels the COMT sites in periphery; (6) its uptake in mouse organs known to have high COMT can be blocked with unlabeled Ro41-0960.

In Fiscal Year 1996, we have the following technical progress and results. In order to further characterize the ability of [^{18}F]Ro41-0960 as a radiotracer to examine COMT activity in the peripheral organs, we carried out detailed pharmacological studies in both baboons and mice which are summarized in the following sections and include: (1) dynamic scanning on baboon kidney and liver with PET, including pharmacological blocking studies with unlabeled Ro41-0960 to assess if the binding of [^{18}F]Ro41-0960 on COMT sites is saturable and sensitive to inhibition of COMT; (2) kinetic modeling using Patlak graphic analysis on uptake data in liver and kidney; (3) measurements of unchanged [^{18}F]Ro41-0960 in baboon plasma using HPLC; (4) dose-dependent inhibition studies of unlabeled Ro41-0960 on the uptake of [^{18}F]Ro41-0960 in mice; (5) displacement studies of unlabeled Ro41-0960 after injection of [^{18}F]Ro41-0960 in mice; (6) HPLC metabolite analysis of mouse tissues.

(1) Baboon Kidney/Liver Studies: Baboons ($n = 2$) were injected intravenously with [^{18}F]Ro41-0960 alone (control) or pretreated intravenously with unlabeled Ro41-0960 (2 mg/kg) at 30 min, 2.5 hrs, 5.3 hrs, or 30 hrs before radiotracer injection. For each study, the baboon was positioned such that kidney and liver could be dynamically scanned at the same time. Time-activity curves of [^{18}F]Ro41-0960 at baseline in the kidney and liver are shown in Figure 1. The pretreatment studies (4 different time intervals) indicated a slow recovery to baseline for both liver and kidney at 5 hrs after pretreatment (data not shown). This trend was also indicated by comparing the influx constants K_i for the five studies (see data analysis below).

Figure 1. Time-activity Curves of [^{18}F]Ro41-0960 at baseline in the Kidney (solid squares) and Liver (open circles).

(2) Data Analysis of Baboon liver and kidney Studies: Uptake data in liver and kidney with [^{18}F]Ro41-0960 was analyzed in terms of an influx constant K_i (Patlak and Blasberg, 1985; Patlak, et al., 1983) determined from

$$A(t)/Cp(t) = K_i \int_0^t Cp(t)dt / Cp(t) = V_i$$

where $A(t)$ is the tissue radioactivity at time t and $Cp(t)$ is the plasma radioactivity of Ro41-0960 at time t , K_i is the slope of the linear portion of the curve and V_i is the intercept. The plot of

$$A(t)/Cp(t) \text{ vs } \int_0^t Cp(t)dt / Cp(t)$$

was found to have a linear portion for both tissues for times greater than 20 min indicating that the labeled ligand was essentially trapped for the duration of the experiment, approx. 1 hr. Although the compound is not strictly irreversibly bound, its dissociation from the enzyme appears to be sufficiently slow to allow calculation of an influx constant. That K_i is associated with uptake by the enzyme is consistent with the fact that pretreatment with unlabeled compound at 30 min prior to the radiotracer injection greatly reduced the measured value

of K_i from 0.017 at baseline to approx. 0.0 ml/min/g in liver. The recovery to baseline is slow, at 2.5 hrs after pretreatment $K_i = 0.002$ and at 5 hrs $K_i = 0.006$ (Figure 2). Similar results were found for the kidney. These studies suggest that the binding of [^{18}F]Ro41-0960 to COMT sites in periphery is saturable and sensitive to inhibition of COMT. It also demonstrates that measurably large changes in tracer uptake (and K_i) were observed.

Figure 2: Graphical analysis (Patlak, et al., 1983) of Baboon Liver Time-activity Data with [^{18}F]Ro41-0960. K_i (influx constant), the slope of the linear portion of the curve, can thus be calculated. Control (open circle, $K_i = 0.0175$); pretreatment with unlabeled Ro41-0960 prior the tracer injection at 30 min (cross, $K_i = 0$); 2.5 hrs (solid square, $K_i = 0.002$); 5.3 hrs (solid circles, $K_i = 0.006$); and 30 hrs (open square, $K_i = 0.0096$). The unit for K_i is ml/min/g. Note the slow recovery of K_i values after pretreatment to the K_i value of baseline.

(3) HPLC Analysis of Baboon Plasma: In the case of the NCA study, assay of the fraction of unchanged [^{18}F]Ro41-0960 in baboon plasma by HPLC (Phenomenex, Spherex 5 μ C-18 column 4.6 x 250 mm, eluted with acetonitrile/0.01M $\text{H}_3\text{PO}_4 = 50/50$ at flow 0.8 mL/min) gave 94%, 84%, 73%, 53%, and 23% at 1, 10, 30, 60, and 84 min, respectively, and the metabolite eluted at the

void volume increased with time. In the case of the CA study, [^{18}F]Ro41-0960 was metabolized faster; assay of the fraction of unchanged [^{18}F]Ro41-0960 gave 88%, 50%, 26%, 21% and 16% at 1, 10, 30, 60, and 84 min, respectively.

(4) Dose-dependent Inhibition Studies in Mice: Mice were injected intravenously with [^{18}F]Ro41-0960 (5 μCi) along with saline (control) or unlabeled Ro41-0960 at three different doses (0.1, 1.0 or 10 mg/kg) ($n = 4$ per group, total 4 groups). After 30 min, mice were sacrificed.

The effect of dilution of intravenously administered [^{18}F]Ro41-0960 with unlabeled Ro41-0960 (0.1, 1.0, or 10 mg/kg) was shown in Table 1. There was little effect of 0.1 mg/kg or 1 mg/kg Ro41-0960 on F-18 concentrations in blood, brain or liver. However, the kidney concentration decreased dose-dependently from 16.3 ± 1.4 %IA/g in control animals, to 6.0 ± 1.1 %IA/g at 1 mg/kg. At 10 mg/kg, kidney F-18 decreased further to 2 %IA/g; F-18 in blood, brain and liver also fell dramatically.

Table 1: Dose-dependent Inhibition of Unlabeled Ro41-0960 (0.1, 1.0, and 10 mg/kg) on the Uptake of [^{18}F]Ro41-0960 in Blood, Brain, Liver and Kidney.

%IA/g	Control	0.1 mg/kg	1.0 mg/kg	10 mg/kg
Blood	8.45 ± 1.02	—	8.97 ± 2.58	$1.88 \pm 0.50^*$
Brain	0.33 ± 0.10	0.35 ± 0.09	0.31 ± 0.05	$0.11 \pm 0.01^*$
Liver	8.95 ± 0.44	9.92 ± 1.23	10.22 ± 1.29	$4.18 \pm 1.11^*$
Kidney	16.27 ± 1.41	12.47 ± 0.80	6.03 ± 1.13	$2.00 \pm 0.57^*$

*Indicates significant differences ($p < 0.01$) as compared to the control values by one-way ANOVA analysis.

(5) Displacement Studies: Two groups of mice were studied ($n = 5$ per group). In the

first group, [^{18}F]Ro41-0960 (5 μCi) was injected intravenously and 5 min later saline was injected (i.v.). Animals were sacrificed 30 min later. In the second group, unlabeled Ro41-0960 (10 mg/kg) was given instead of saline and the same procedure followed.

The administration of unlabeled Ro41-0960 resulted in the displacement of radioactivity from most organs sampled. F-18 concentrations in blood, brain, heart, lungs, kidneys, and spleen were 33-45% lower than in control animals; F-18 in liver fell 20%. The displacement in these organs was significant ($p < 0.01$). However, F-18 was increased after drug treatment in small intestine (3.5% to 7.1%IA/g) and urine (43% to 68%IA/g, data not shown), probably due to drug effects on excretion pathways (Figure 3).

Figure 3: Displacement of [^{18}F]Ro41-0960 with Unlabeled Ro41-0960 (10 mg/kg) at 5 min Post Injection. Control (gray bars); drug treated (dark bars). BL (blood); BR (brain); HT (heart); LU (lung); LI (liver); KI (kidney); INT (intestine); STM (stomach); SP (spleen). * uptake in the brain was less than 0.5%IA/g.

(6) HPLC Metabolite Analysis of Tissues: Mice were sacrificed 30 minutes after intravenous injection of [^{18}F]Ro41-0960 along with saline or unlabeled Ro41-0960 (10 mg/kg). The blood, whole brain, and one kidney, from each animal were homogenized,

sonicated and centrifuged. The supernatants were analyzed by HPLC as described above for baboon plasma.

The results of HPLC analysis are presented in Table 2. HPLC analyses of plasma following administration of [^{18}F]Ro41-0960 were qualitatively similar in baboons and mice. The peak that eluted at the void volume appeared to be the conjugates of Ro41-0960 resulting from glucuronidation; the peak eluted after [^{18}F]Ro41-0960 corresponded to the methylated metabolite which was identified by comparison with the retention time of the authentic compound on the HPLC. These metabolites have been shown to lack activity as inhibitors of COMT.

Table 2: HPLC Analysis of Tissues at 30 min after Injection of [^{18}F]Ro41-0960 for NCA Studies and CA Studies [1.4 mg/kg (for baboon) or 10 mg/kg (for mouse) of Unlabeled Ro41-0960 Coinjected with [^{18}F]Ro41-0960].

Tissue	Void volume (%)	Ro41-0960 peak (%)	Late peak (%)	Extraction efficiency (%)
Baboon				
Plasma NCA	17	73	--	83
Plasma CA	55	26	--	81
Mouse				
Plasma NCA	2	12	86	88
Plasma CA	1	77	8	81
Brain NCA	6	14	74	89
Brain CA	7	67	13	91
Kidney NCA	8	70	13	94
Kidney CA	76	7	6	95

Differing percentages of unchanged [^{18}F]Ro41-0960 in baboon and mouse plasma at 30 min after injection of NCA [^{18}F]Ro41-0960 are probably due to faster metabolism in

the smaller animal. The late metabolite (methylated Ro41-0960) was the predominant labeled compound in the mouse, whereas only a trace was found in baboon plasma. Addition of carrier Ro41-0960 to the injected [^{18}F]Ro41-0960 resulted in an increased fraction of unchanged [^{18}F]Ro41-0960 in the mouse but a decreased fraction in the baboon. The increase in the mouse could be due to saturation of the capacity to methylate Ro41-0960. The decrease in unchanged tracer with carrier in the baboon is associated with increased fractional radioactivity at the void volume (polar conjugated metabolite(s)), and could be due to easier extraction of CA than NCA [^{18}F]Ro41-0960 at the site(s) of conjugation. The average brain to blood ratio for mice (n=12) was 0.04, which is similar to the known fractional blood content of this organ. This finding, together with the similarity of the HPLC metabolite patterns observed for brain and blood, provides convincing evidence that most of F-18 in the brain after administration of [^{18}F]Ro41-0960 represents F-18 in the brain vasculature. The fact that most F-18 in the kidney from NCA studies was largely as [^{18}F]Ro41-0960 suggests that the PET imaging of baboon kidney was due to the unchanged [^{18}F]Ro41-0960 rather than its metabolite(s).

Our studies demonstrate that (1) we can synthesize [^{18}F]Ro41-0960 in sufficient yield for PET studies; (2) [^{18}F]Ro41-0960 has low cerebral bioavailability, in contrast, to the many claims of its central activity in the literature; (3) tracer uptake is highest in kidney and liver which is consistent with high levels of COMT in these peripheral organs; (4) it labels the COMT sites in periphery and is sensitive to inhibition of COMT; (5) its uptake in mouse organs known to have high COMT can be displaced with unlabeled Ro41-0960; (6) the F-18 activity in kidney is unchanged [^{18}F]Ro41-0960. These studies support the proposal which was just awarded

by National Institutes of Health NIH/NINDS, 1996-2001 (First Independent Research Support and Transition Award (FIRST-R29) on "PET Studies of Catechol-O-Methyltransferase") to (1) further characterize [^{18}F]Ro41-0960 as a tracer for peripheral COMT *in vivo*; (2) to synthesize and characterize [^{11}C]Ro40-7592, a COMT inhibitor used clinically to treat PD; and (3) to examine the pharmacodynamics of COMT inhibition with PET. These studies will form the groundwork for investigating the role of COMT in disease and will serve as a tool in drug research and development.

PAPERS/JOURNALS/PUBLICATIONS:

Y.-S. Ding, Y. Sugano, S.J. Gatley, J.S. Fowler, J. Koomen, N. Volkow, R. Chen, C. Shea, D.J. Schlyer. Synthesis of [^{18}F]Ro41-0960, a potent COMT inhibitor, for use in *in vivo* mapping with PET. 42nd Society of Nuclear Medicine Meeting (Abstract), June 1995.

Y.-S. Ding, S.J. Gatley, J.S. Fowler, R. Chen, N.D. Volkow, J. Logan, C.E. Shea, Y. Sugano, J. Koomen. PET Radiotracers for Studies of Catechol-O-Methyltransferase. 11th International Symposium on Radiopharmaceutical Chemistry (Abstract), August 1995.

Y.-S. Ding, S.J. Gatley, J.S. Fowler, R. Chen, N.D. Volkow, J. Logan, C.E. Shea, Y. Sugano, J. Koomen. Mapping Catechol-O-Methyltransferase *in vivo*: Initial Studies with [^{18}F]Ro41-0960. *Life Sciences*. 58,195-208,1996

Y.-S. Ding, Y. Sugano, J.S. Fowler, J. Koomen, D. Aggarwal, R. Synthesis of [^{18}F]Ro41-0960, a potent Catechol-O-Methyltransferase inhibitor, for PET studies. *J. Label. Compd. Radiopharm.* submitted, 1996

Y.-S. Ding, S.J. Gatley, J.S. Fowler, R. Chen, N.D. Volkow, J. Logan, Y. Sugano, J. Koomen. Mapping Catechol-*O*-Methyltransferase *in vivo* with [¹⁸F]Ro41-0960. The Eighth International Catecholamine Symposium (oral presentation), October 13-18, 1996.

FOLLOW-ON FUNDING:

First Independent Research Support and

Transition Award (FIRST-R29), "PET Studies of Catechol-*O*-Methyltransferase" National Institute of Health NIH/NINDS, 1996-2001.

LDRD FUNDING:

FY 1995	\$ 98,779
FY 1996	\$102,807

Note: This project involves animal vertebrates or human subjects.

Development of Intense, Tunable 20-femtosecond Laser Systems

Edward Castner, Jr.

95-11

PROJECT DESCRIPTION:

Novel ultrashort pulse laser systems producing pulse durations less than 20 femtoseconds (2.0×10^{-14} s) are being designed and built at BNL. To apply such ultrashort laser pulses to the study of real-time photochemistry and photophysics, we are developing new time-resolved absorption and emission spectrometers. These laser systems and spectrometers are being used to initiate and probe some of the most rapid photochemical reactions yet discovered in solution.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: To fully understand chemical reaction dynamics in solution it is necessary to understand all of the inter- and intramolecular relaxation pathways available to a light-absorbing chromophore after photoexcitation. These processes include coupling between the different vibrational modes within the molecule, non-radiative pathways including internal conversion from higher-lying to lower energy excited states, intersystem crossing (or a jump between molecular quantum states of differing electronic spin multiplicities), and solvation dynamics: the coupling between these time-evolving quantum states of the chromophore molecule with the density fluctuations, collisions, and librational motions of the surrounding solvent molecules.

Approach: Certain photochemical reactions can only be studied in the time domain, because the reaction intermediates, and sometimes even the reaction products have lifetimes less than one picosecond (10^{-12} s). At the same time, some of these very rapid reactions are among the most important chemical reactions. Specifically, the primary step in the bacterial photosynthesis cycle is a photo-induced electron-transfer that occurs in 200 fs. The primary process in the chemistry of vision is a photo-induced isomerization reaction, which is also complete in 200 fs.

By using a femtosecond laser pulse to prepare a coherent superposition of molecular quantum states of a photoreactive molecule in solution, we can directly probe the rapid relaxation processes of internal conversion, intersystem crossing, dynamical solvation, and photo-induced reactions. In our lab, this is done by measuring the absorption or emission spectrum from either the reactants or products as a function of delay time after photoexcitation. However, the molecular dynamics are occurring on a time scale competitive with molecular vibrations and rotations (10-2500 femtoseconds), so these ultrafast dynamics cannot be detected by even the fastest electronic instrumentation. Instead, we make use of the short duration of the actinic laser pulse to provide the time resolution via an optical-optical correlation experiment. By splitting a fraction of the actinic pulse, the second fraction of the light pulse is used to generate a white-light supercontinuum with which to probe the transient absorption spectrum of the photo-reacting system. Alternatively, if we require the ultrafast emission spectrum, we can use the second fraction of the actinic laser pulse as a trigger for a nonlinear optical time gating. In either case, the limiting time resolution is ultimately determined by the duration of the laser pulse.

Technical Progress and Results: The two-color femtosecond transient absorption spectrometer describe in the FY 1995 LDRD report has been completed. Using this instrument, studies of several important photochemical and photophysical processes have been carried out. We have measured the internal conversion from a higher-lying singlet excited state (the Soret band) to a lower energy singlet state (Q-band) of Co(II)octaethylporphyrin in toluene and methylene chloride solution. This intramolecular electronic relaxation process is found to occur in about 1 picosecond. In another project, the intersystem crossing, or electronic spin state conversion of Ru(II)(bpy)₃ has been measured. One of the most widely studies model systems in inorganic photochemistry and solar photo-conversion research, the Ru(II)(bpy)₃ triplet metal-to-ligand charge-transfer (MLCT) state is obtained after excitation of the singlet electronic transition via intersystem crossing. We find evidence that this spin state interconversion occurs in <300 fs. A third project has been to examine the electron-radical geminate recombination reaction for a series of aromatic amines (such as N,N-dimethyl-aniline) produced by multi-photon ionization in the neat liquid).

The femtosecond fluorescence upconversion instrument mentioned in the FY 1995 report has been completed. Using tunable second-harmonic excitation pulses from a Ti:sapphire laser, excitation wavelengths ranging from 375-450 nm are routinely accessible. Because the optical design of the spectrometer incorporates an all-reflective ellipsoidal metal-coated reflector, the collimation and focusing of the molecular emission is free from group-velocity dispersion effects. Because of careful control of the group-velocity dispersion, typical pulse resolutions are 80 fs, and with careful data analysis by iterative

reconvolution nonlinear least-squares fitting, molecular photoemission dynamics with time constants less than 40 fs can be resolved.

The newly completed upconversion instrument has been applied to the study of two fundamental problems in photo-induced electron-transfer phenomena in solution. The first is the case where a photo-induced bimolecular electron-transfer reaction occurs between the solvent (electron donor) and the excited-state of a photo-excited acceptor molecule. The second case is when an electron is transferred from the excited state of a photosensitizing dye molecule (adsorbed onto the surface of a semiconductor nanocrystal in solution) into the conduction band of the semiconductor. In both cases, the most rapid electron-transfer processes are occurring within the time range of 25-500 fs, a time scale which can only be probed by this technique.

In the first case, photo-induced electron-transfer occurs after excitation of a coumarin molecule to its first singlet excited state, with the electron-donation occurring from an aromatic amine, such as N,N-dimethyl-*para*-toluidine. The reactants and products in this photoreaction are shown in Figure 1. Key features of this bimolecular electron-transfer reaction are that there are about 18-20 solvent molecules in contact with the coumarin chromophore, and that each solvent molecule is a potential electron-donor. The rate of the reaction is determined by the free-energy driving force between reactants and products; and by the electronic coupling, determined by the degree of overlap between donor and acceptor molecular orbitals. For the example shown below, the effective rate of electron-transfer of 3.3 ps⁻¹ is obtained from the rapid decay of the coumarin emission, which is quenched by a factor of about 10⁴ relative to its natural radiative decay in a non-electron-donating solvent. A typical data set is shown

in Figure 2. However, in addition to directly measuring the rates of some of the fastest bimolecular electron-transfer reactions known, the fluorescence decay profile provides evidence at the earliest times of a lag, or rise-time, indicative of the inertial solvent response. More specifically, the dynamical solvation about the excited state of the molecule occurs even more rapidly than the very fast electron-transfer. Intermolecular librations between solvent molecules with a frequency of about 65 cm^{-1} begin to stabilize the charge distribution of the coumarin excited state, with a rise time of 115 fs, all prior to the most rapid and largest amplitude (92%) decay process which has a time constant of 220 fs. These data provide clear evidence that a two-dimensional reaction coordinate describing the electron-transfer process must be used. This series of experiments provides clear evidence that a multi-dimensional model for this class of reactions is required, in which the reaction coordinate competes with other excited-state pathways, including dynamical solvation and vibrational relaxation.

Another series of experiments were performed with the fluorescence upconversion instrument, which were possible only because of the outstanding time resolution achieved. In this case, a carboxylic acid functional group on a coumarin dye was tethered to the surface of a semiconductor nanocrystal in solution, such as TiO_2 or ZnO . In the photo-excited

state of the coumarin in this configuration, the coumarin becomes an electron donor. The excited-state of the coumarin is quenched when it gives up an electron into the conduction band of the semiconductor. In ZnO , the reaction is not particularly rapid, occurring on the time scale of tens of picoseconds. However, for TiO_2 nanocrystals of 50 Å diameter in water, the forward electron-transfer event is occurring within <50 fs after photoexcitation.

Quite exciting results have already been obtained with the new femtosecond transient absorption and fluorescence upconversion spectrometers. These spectrometers will now become primary tools for investigating the short time dynamics in photo-induced electron-transfer reactions in solution.

PAPERS/JOURNALS/PUBLICATIONS:

The first results from the femtosecond bimolecular photo-induced electron-transfer project (see Figure 2) were presented during an invited talk at the 20th DOE Solar Photochemistry Research Conference (June 8-12, 1996, French Lick, IN). The manuscripts for three articles are in preparation.

LDRD FUNDING:

FY 1995	\$66,937
FY 1996	\$64,605

Photo-induced electron-transfer from solvent donor to excited-state acceptor:
E.g., Coumarin 152 in *N,N*-dimethyl-*para*-toluidine

Figure 1. Ultrafast photo-induced electron-transfer to a Coumarin 152 (4-trifluoromethyl, 7-dimethylaminocoumarin) acceptor from a *N,N*-dimethyl-*p*-toluidine donor. The effective rate constant is $k_{\text{eff}} = 3.3 \times 10^{12} \text{ s}^{-1}$.

Figure 2. Ultrafast fluorescence dynamics for the photo-induced electron-transfer reaction between *N,N*-dimethyl-*p*-toluidine and Coumarin 152. Residuals to a four-exponential fit are shown at top; data (dots) and fit (solid line) are shown below.

Use of Extreme Thermophilic Bacterium *Thermotoga Maritima* as a Source of Ribosomal Components and Translation Factors for Structural Studies

*F. William Studier and
Venki Ramakrishnan*

95-13

PROJECT DESCRIPTION:

We are engaged in a long-term study of the ribosome, and in particular in the crystallography of ribosomal proteins, initiation factors (IF) and peptide chain release factors (RF). It has been the general experience that thermophilic bacteria yield proteins that are more easily crystallizable than those of mesophilic organisms such as *Escherichia coli*. In order to investigate the possibility of working on extremely thermostable proteins, we decided to use the organism *Thermotoga maritima*, which is a eubacterium unlike the other hyperthermophiles, and is closely related to bacteria such as *E. coli*. However, it can grow at the astonishingly high temperature of 90°C.

We have recently begun structural studies on the intact translational initiation factor IF3 isolated from *T. maritima* with the goal of crystallizing it. In addition, we are interested in identifying one or more of the peptide chain release factors (RF-1, RF-3 and RF-3) from *T. maritima* to begin structural studies of these proteins.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Approach: Rather than trying to purify the peptide chain release factors from large amounts of *T. maritima* cells, we decided to clone their genes and overexpress them in *E. coli*.

Once the gene sequences have been determined, the gene will be transferred to one of the T7-based expression vectors developed at Brookhaven, pET-13a. Then genes can then be expressed to high levels upon induction in the strain BL21(DE3).

Technical Progress and Results: A comparison of the sequence of various prokaryotic peptide release factors reveals several highly conserved stretches of amino acids. The sequence of these regions were used to design degenerate oligonucleotide primers. PCR amplification of *T. maritima* genomic DNA using pairs of primers yielded several discrete bands that were cloned for sequence analysis. If any of these represent regions of *T. maritima* RF's, we will use them to probe restriction digested genomic *T. maritima* DNA to clone the full-length versions of these genes.

PAPERS/JOURNALS/PUBLICATIONS:

The results will be included in comprehensive publications when crystals of *T. maritima* IF3 and RF's are obtained.

LDRD FUNDING:

FY 1995	\$92,696
FY 1996	\$96,402

Biochemical and Structural Studies of Chaperon Proteins from *Thermotoga Maritima*

John M. Flanagan

95-15

PROJECT DESCRIPTION:

High resolution structural studies of the Hsp70 chaperone system from thermophilic bacteria.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: The Hsp70 chaperone system is comprised of three proteins: Hsp70, Hsp40, and Hsp20. Homologues of the Hsp70 system are found in all organelles and cell types, and the system is thought to play key roles in the cellular protein folding process. *In vitro*, protein folding occurs spontaneously, and proceeds to the thermodynamic minimum state. In contrast, the folding of many proteins, *in vivo*, requires the assistance of molecular chaperones that aid this process, but are not themselves incorporated into the final folded state. A detailed mechanism for the action of molecular chaperones in assisting folding is not known, however, most current models hold that chaperones act to minimize "off-pathway," non-specific protein-protein interactions that lead to aggregation. Very little is known about the three-dimensional structures of the components in the Hsp70 molecular chaperone system, or for their complexes. To date, only the structures of the ATPase domain of Hsp70, and the J-homology domain of Hsp40 are known. These studies have provided important clues to the mechanism of Hsp70 and Hsp40 action, although additional structural information will be required to fully understand these important proteins.

Approach: The three-dimensional structure of a protein can be determined either by NMR spectroscopy, or by single crystal X-ray diffraction. The relatively large size of the individual components in the Hsp70 chaperone system limits their study by NMR spectroscopy, and X-ray diffraction studies are hampered by the lack of suitable crystals. Some of the difficulties in crystallizing these proteins may be related to their specific functions. First, both Hsp70 and Hsp40 possess protein binding activities that result in their aggregation at high concentrations. In addition, both Hsp70 and Hsp40 are multi-domain proteins, and biochemical evidence indicates that the links between domains are relatively flexible. To circumvent these problems, studies were initiated to identify, clone, and over express, in *Escherichia coli*, thermophilic homologues of Hsp70, Hsp40, Hsp20. The thermophilic homologues may be better suited for crystallization trials, in part, because these experiments are conducted in a range of temperatures (4 to 25°C) far from the optimum temperatures (70 to 90°C) for their activity.

Two approaches are being employed to identify the genes encoding the Hsp70 system from three thermophilic bacteria: *Thermotoga maritima* (TM), *Thermus thermophilus* (Tth), and *Bacillus stearothermophilus* (Bst). One approach is to design degenerate oligonucleotide primers that are complimentary to the DNA sequence encoding 7-10 residue long stretches of absolutely conserved amino acids. These oligonucleotides are used to amplify regions of the genomic DNA of the organism by PCR. The amplified PCR products can then be used to screen a genomic library from this organism. The second approach is based upon the high degree of functional conservation in the Hsp70 system. Specifically, Hsp70 and Hsp20 form a tight complex involving highly conserved residues that are not contiguous in

the linear amino acid sequence. However, the high degree of functional conservation in these two proteins means that heterologous complexes, containing Hsp70's from one species and Hsp20's from another, can be formed, and provides a means to identify Hsp20 homologues from various sources. To date, both approaches have been tried with limited success.

Technical Progress and Results: We have successfully cloned homologues of DnaK, DnaJ, and GrpE from *Tth*. The genes encoding the DnaK chaperone system are organized in a cluster containing at least five genes in the order dnaK-dnaJ-grpE-orf4-clpB. The reading frames of dnaJ and orf4 overlap by 11 bases, and clpB genes starts after a 61-base intergenic sequence. The putative 8kDa protein encoded by orf4 is not homologous to any known protein in the Swiss protein data base and its function is currently unknown. We have currently cloned the dnaK, dnaJ, and grpE genes into the T7-based pET *E. coli* expression vectors. Both the dnaK and grpE genes are highly homologous to the dnaK and grpE genes in *E. coli*, while the *Tth* dnaJ homologue more closely resembles another the second dnaJ-like protein of *E. coli* cbpA. At the present time we have not identified homologues of the DnaK chaperone system of *Tm* or *Bst*.

Structural studies are being designed to investigate the structure and function of the purified *Tth* DnaK/DnaJ/GrpE homologues.

PAPERS/JOURNALS/PUBLICATIONS:

R. B. Hill, J. M. Flanagan, J. H. Prestegard. ¹H and ¹⁵N Magnetic Resonance Assignments, Secondary Structure, and Tertiary Fold of *E. coli* DnaJ(1-78). *Biochemistry* 34, 5587-5596 (1995).

A. Szabo, R. Korszun, F. U. Hartl, J. M. Flanagan. A zinc finger-like domain of the molecular chaperone DnaJ is involved in binding to denatured protein substrates. *EMBO J.* 15, 408-417. (1996).

K. Huang, J.H. Prestegard, J.M. Flanagan. Role of the glycine phenylalanine rich region of DnaJ in modulating DnaK's ATPase activity. Submitted *J. Mol. Biol.*

FOLLOW-ON FUNDING:

Funds for these studies are being sought from both the National Institute of Health and the Department of Energy.

LDRD FUNDING:

FY 1995	\$75,762
FY 1996	\$98,776

Low Dose Gamma Imaging Facility for *In Vivo* Molecular Medicine

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95-33

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PROJECT DESCRIPTION:

The subject of this LDRD is to develop a Low Dose Gamma Imaging (LDGI) facility at the Medical Department, BNL, utilizing: 1) the existing shielded rooms of the Whole Body Counter (WBC) for reducing the background, and 2) the WBC and a gamma camera equipped with specially designed high-sensitivity collimators to provide high counting sensitivity with acceptable spatial resolution and low background. The facility will be used for certain applications of nuclear medicine imaging in the field of molecular medicine, such as the study of the whole body distribution of radiolabelled growth factors (GFs), which cannot be carried out using a conventional gamma camera because of the camera's limited sensitivity. In the original proposal two pilot studies were proposed using the LDGI facility: 1) assessment of the metabolism of radioiodinated erythropoietin as a representative of GFs, and 2) analysis of lipid synthesis in the liver employing the dual tracer approach with the two fatty acid analogues ^{123}I -oPPA and ^{131}I -pPPA. However, due to delays in the delivery of the collimator, it will be feasible in the remaining term of the project to complete the phantom measurements to evaluate the performance of the gamma camera and to conduct only one of the two pilot studies to demonstrate the capability of the LDGI facility.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: Although the image quality of both planar scintigraphy and SPECT imaging in the range of activities commonly used in clinical studies is not affected by the environmental background, scintigraphy at very low doses with very high sensitivity collimators will be affected by such background. For this purpose we use the WBC room, shielded by 122 cm-thick low-activity concrete and 10 cm-thick low-activity (pre-World War II) steel. Measurements of background using a 15 cm diameter x 5 cm length NaI(Tl) detector indicate that in the 50-1000 keV energy range this shielding reduces the background radiation by a factor of 30. The exact reduction of the background count for a gamma camera installed in the shielded room depends on the camera's own shielding, the crystal size, and the collimator design.

Our research plan has been as follows:

1. Move the Toshiba gamma camera GCA-901A into the shielded room.
2. Design the gamma camera collimators for low dose gamma imaging with very high sensitivity.
3. Evaluate the performance of the gamma camera with newly designed collimators.
4. Carry out one of the two pilot research programs indicated above.

Approach: The collimator was designed to emphasize high counting sensitivity while maintaining an acceptable spatial resolution. Preliminary design of four collimators were made to provide very-high and ultra-high sensitivity for low and medium energy γ -rays.

However, due to the difficulties we encountered with the cost and availability, only one collimator was ordered. It is being manufactured by the Nuclear Fields Corp., Des Plaines, Illinois.

Technical Progress and Results: The new collimator is a parallel-hole lead collimator with a hexagonal array of hexagonal holes optimized for studies using ^{123}I at very high sensitivity (VHS). The septal penetration was designed to be less than 2.5%. Table I compares the expected efficiency of the new collimator with that of the LEGP (low energy general purpose) collimator provided by Toshiba for nuclides emitting gamma rays with energy up to 150 keV. The overall spatial resolutions (FWHM in cm) of these two collimators are presented in Figure 1 as a function of the distance of the source from the collimator face.

The performance of the gamma camera with the new collimator in the shielded room is yet to be evaluated. For certain studies that require shallow organ imaging with very low spatial resolution, we plan to use the gamma camera without any collimator. The spatial resolution in this application will be resulted from the $1/r^2$ dependence of the count-density efficiency on the distance between the source and the camera. The camera will be placed as close as possible to the subject's body. The intrinsic background of the gamma camera in the shielded room was measured and found to be reduced by a factor of 9.

Table I
Comparison of Collimators for ^{123}I

Collimator	LEGP	VHS
Efficiency	2.1×10^{-4}	2.1×10^{-3}
Hole length (cm)	4.0	2.4
Hole diameter (mm)	2.36	4.6
Septum thickness(mm)	0.22	0.65

Figure 1

Overall spatial resolution of the gamma camera as the function of the distance of the source from the collimator face.

LDRD FUNDING:

FY 1995	\$ 109,736
FY 1996	\$ 110,070
FY 1997 (est.)	\$5,000

Note: This project involves animal vertebrates or human subjects.

Atmospheric Degradation of Halogenated Compounds

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95-40

R. Bruce Klemm and

Stuart K. Ross^{††}

PROJECT DESCRIPTION:

The suitability of various alternatives that are needed to replace chlorofluorocarbons (CFCs) and bromine-containing halons (BCHs) must be evaluated by determining the behavior of these compounds prior to their wide spread use in the field. Most of these compounds are not naturally occurring species and have not been widely used in industry. Therefore, the thermochemistry and kinetics of these compounds are rather poorly known. The objective of this LDRD research project is to determine thermochemical properties of some of the CFC and BCH alternatives and their oxidative intermediates and products by using photoionization mass spectroscopy.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: The main thrust of the project has been to determine ionization energies (IEs) and appearance energies (AEs) of selected species, which are then used, in combination with other available thermochemical data to derive heats of formation and bond energies.

Approach: Experiments were performed on a discharge flow-photoionization mass spectrometer (DF-PIMS) apparatus on Beamline U-11 at the NSLS. Threshold energies are determined from photoionization efficiency (PIE) curves which were obtained by scanning over wavelength ranges of interest, at the m/z appropriate for the species under study. While stable compounds were

procured from commercial sources, radical species were generated *in situ* by fast atom-molecule titration reactions. For example, ClO radicals were formed *via* the reaction

where F atoms were produced in a microwave discharge. Measurements of compounds with well known IEs usually preceded experiments on unknown species in order to corroborate the wavelength calibration of the U-11 monochromator and to validate the experimental approach and conditions.

Technical Progress and Results: In our interim report, last year, we reported an attempt to measure the PIE curve and IE for CF_3O which we tried to generate *via* the reaction sequence:

Although both of these reactions are known to be quite fast, with rate constants of about $1 \times 10^{-11} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$ and $2.5 \times 10^{-11} - 1.7 \times 10^{-12} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$, respectively, our attempt to produce CF_3O failed to provide observable signal for CF_3O cation. Subsequent attempts to generate CF_3 by other methods (e.g., $\text{F} + \text{CF}_3\text{H} \rightarrow \text{CF}_3 + \text{HF}$ and microwave discharge of CF_4) also failed to produce viable results. Unless there are unknown problems with the available kinetic studies of reactions (2) and (3), our negative result suggests that CF_3O^+ may not be stable. Rather, it probably undergoes rapid dissociation to produce fragmentation ions. Further study will be required to search for these predicted ions, which might include CF_2O^+ .

Experimental results, obtained for IE(HOI) and IE(IO), were mentioned in the interim report for FY1995 but not stated

explicitly. For HOI, we measured an IE of $9.8_1 \pm 0.02_0$ eV (average of eight individual determinations) that corresponds to the $\text{HOI}^+(\text{X}^2\text{A}') - \text{HOI}(\text{X}^1\text{A}')$ transition. In addition, we determined the HO-I stretching frequency in the cation to be $702 \pm 60 \text{ cm}^{-1}$. For IO, we measured an IE of $9.73_5 \pm 0.01_7$ eV (average of ten individual determinations) that corresponds to the $\text{IO}^+(\text{X}^3\Sigma^-) - \text{IO}(\text{X}^2\Pi^{3/2})$ transition. The vibrational spacing in the cation was determined to be $1060 \pm 60 \text{ cm}^{-1}$. In addition, a selected value for $D^0_0(\text{IO})$ [226 kJ mol^{-1}] was used to derive a value for $\Delta_f H^0_0(\text{IO})$ [$\approx 128 \pm 4 \text{ kJ mol}^{-1}$] and to obtain estimates for the $\Delta_f H^0_0(\text{IO}^+)$ [$\approx 1067 \text{ kJ mol}^{-1}$], $\Delta_f H^0_0(\text{HOI})$ [$-42.7 \text{ kJ mol}^{-1}$] and the proton affinity of IO [$752 \pm 10 \text{ kJ mol}^{-1}$]. The measurements of IE(HOI) and IE(IO) are the first experimental values to be reported and we are pleased to note that our IE(HOI) result was just recently confirmed by high level calculations (reported by other investigators).

Iodine-containing halons have been suggested as possible alternatives to replace BCH fire suppressants. Chlorinated and brominated compounds are known to degrade in the stratosphere producing Cl and Br atoms respectively. These atoms react with stratospheric ozone and are recycled in a series of reactions involving ClO\BrO

where X = Cl or Br.

It is believed, in the absence of sufficient experimental evidence, that iodine may be potentially more efficient at destroying ozone than Cl and Br, thus the impact on ozone depletion may be significant even if only very small quantities of iodine compounds are

transported into the stratosphere. In our investigations we have measured IEs and determined or estimated heats of formation of the halogen monoxide series.

Species	IE (eV)	$\Delta_f H^0_{298} (\text{kJ mol}^{-1})$
IO	9.74 ^a	126 ^b
BrO	10.46 ^a	125.8 ^c
ClO	10.89 ^a	101.6 ^c
FO	12.78 ^a	109.5 ^a

a - measured or derived at BNL
b - estimated c - literature values

The IE measurements in the table above were all performed at BNL and they represent the first direct determinations via photoionization mass spectroscopy for these halogen monoxides.

The ionization energy values for BrO and ClO, determined in this work, were immediately useful in follow-up studies on the dissociative ionization of Br₂O and Cl₂O. The appearance energies of BrO⁺ (from Br₂O) and ClO⁺ (from Cl₂O) were measured and used to derive enthalpies of formation for Br₂O and Cl₂O. The values determined were $\Delta_f H^0_{298}(\text{Br}_2\text{O}) = 107.1 \text{ kJ mol}^{-1}$ and $\Delta_f H^0_{298}(\text{Cl}_2\text{O}) = 77.18 \text{ kJ mol}^{-1}$. Additionally, the enthalpies of these dihalogen oxides are coupled (at equilibrium) to their respective hypohalous acids (HOBr, HOCl) through the reaction with water, e.g., $\text{Br}_2\text{O} + \text{H}_2\text{O} \rightleftharpoons 2\text{HOBr}$. Therefore, from reported values for the equilibrium constants and our own derived values for the enthalpies of Br₂O and Cl₂O, we readily determined enthalpies for HOBr and HOCl: $\Delta_f H^0_{298}(\text{HOBr}) = -60.0 \text{ kJ mol}^{-1}$; $\Delta_f H^0_{298}(\text{HOCl}) = -76.8 \text{ kJ mol}^{-1}$. Only two years ago, the heats of formation of Br₂O, Cl₂O, HOBr and HOCl were generally not well known because a very wide range of values existed in the literature. With our reports on the IEs and enthalpies of these

species, $\Delta_f H^\circ_{298}$ for these compounds are now firmly established.

The PIE curves of several perfluorinated carbons (PFC) and hydrofluorinated carbons (HFC) were measured along with PIE curves of the fragment cations from these PFCs and HFCs. The compounds studied were CH_3CF_3 ; $\text{CHF}_2\text{CH}_2\text{F}$, C_2F_6 ; and C_3F_8 . Fragment cations, formed *via* dissociative ionization were (source compounds in parentheses): CF_3^+ , CH_3^+ (CH_3CF_3); CFH_2^+ , CF_2H^+ ($\text{CHF}_2\text{CH}_2\text{F}$); CF_3^+ , C_2F_5^+ (C_2F_6); and CF_3^+ , C_2F_4^+ , C_2F_5^+ , C_2F_6^+ (C_3F_8). This work is a combined experimental and theoretical study and it requires numerous calculations before it can be completed. However, the observation of C_2F_6^+ and C_3F_8^+ in this study appears to be the first time these cations have been detected. Both compounds are known to be dissociatively ionized with high efficiency; and, indeed, in this study, the fraction of molecular cation signal to fragment ion signal was only about 1 part in 1000. Therefore, it is not surprising that the molecular cations had gone undetected until now because laboratory light sources are typically 100 to 1000 times less intense in the extreme ultraviolet than the U-11 beam-line light source. The experimental IEs of C_2F_6 and C_3F_8 are about 12.85 eV and 12.65 eV, respectively. These results are in reasonable agreement with preliminary calculations (using electronic structure analysis methods/Gaussian 92).

PAPERS/JOURNALS/PUBLICATIONS:

P.S. Monks, L.J. Stief, D.C. Tardy, J.F. Liebman, Z. Zhang, S.C. Kuo and R.B. Klemm, "Discharge Flow-Photoionization Mass Spectrometric Study of HOI: Photoionization Efficiency Spectrum and Ionization Energy," *J. Phys. Chem.*, **99**, 16566 (1995).

Z. Zhang, P.S. Monks, L.J. Stief, J.F. Liebman, R.E. Huie, S.C. Kuo and R.B. Klemm, "Experimental Determination of the Ionization Energy of $\text{IO}(\text{X}^2\Pi_{3/2})$ and Estimations of $\Delta_f H^\circ_0(\text{IO}^+)$ and $\text{PA}(\text{IO})$," *J. Phys. Chem.*, **100**, 63 (1996).

R.P. Thorn, Jr., P.S. Monks, L.J. Stief, S.C. Kuo, Z. Zhang and R.B. Klemm, "Photoionization Efficiency Spectrum, Ionization Energy," and Heat of Formation of Br_2O , *J. Phys. Chem.*, **100**, 12199 (1996).

R.P. Thorn, Jr., L.J. Stief, S.C. Kuo and R.B. Klemm, "The Ionization Energy of Cl_2O and ClO , Appearance Energy of $\text{ClO}^+(\text{Cl}_2\text{O})$ and Heat of Formation of Cl_2O ," *J. Phys. Chem.*, **100**, 14178 (1996).

LDRD FUNDING:

FY 1995	\$94,245
FY 1996	\$36,369

† Research Associate (left the project on 20 October, 1995).

†† Visiting Research Associate (July - November 1996).

Extraction and Destruction of Hazardous and Toxic Chemical Pollutants During Soil/Sludge Remediation Using Innovative Technologies

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95-44

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PROJECT DESCRIPTION:

The objective of this research is to develop a new remediation technology for soils/sludges contaminated with various toxic and hazardous organic pollutants using cyclodextrins. Since cyclodextrins are environmentally friendly, non-toxic, non-hazardous and readily form complexes with various organic compounds, their use for environmental remediation was examined. The biodegradation of organic pollutants in the presence of cyclodextrin was investigated as cyclodextrins can potentially enhance the biodegradation of recalcitrant compounds by cometabolism.

TECHNICAL PROGRESS AND RESULTS - Fiscal Years 1995 & 1996:

Purpose: The remediation of soils contaminated with various toxic and hazardous organic compounds is a major environmental concern. At present, there are numerous contaminated sites across the country requiring clean up and remediation. In the US alone, it is estimated that the cost of remediating most of the Superfund and Resource Conservation and Recovery Act (RCRA) sites is about \$750 billion and this cost is expected to increase in the future. Therefore, it is imperative to develop cost-

effective technologies which can address the enormous problem of soil remediation to protect human health and the environment.

One of the technologies to remediate contaminated soils is the soil washing/flushing technique. With this technique, surfactants (cationic, anionic or neutral) either alone or in combination with acids, bases, or complexing agents are used. However, the surfactant technique suffers from many drawbacks such as (a) the chemicals used for remediation are themselves toxic and corrosive making the remediated soil unfit for reuse, (b) forms high viscosity emulsions that are difficult to separate, (c) sorption of surfactant by the soil which means that more extractant is needed for extraction, and (d) inability to recover the surfactant for recycling. Therefore, it is desirable to develop new techniques that can overcome the problems associated with the soil washing surfactant method.

Approach: Cyclodextrins are cyclic oligosaccharides comprising of six, seven and eight glucopyranose units, and are called as α -, β -, and γ - cyclodextrins, respectively. Cyclodextrins are obtained by microbial enzymatic degradation of starch and are commercially available. The shape of the cyclodextrin molecule is a half truncated cone with a cavity inside. The outer periphery of the molecule is hydrophilic while the interior of the cavity is apolar and hydrophobic in nature. Because of this unique structural feature, cyclodextrins form inclusion complexes with non-polar organic compounds such as polynuclear aromatics (PNAs), organochlorine pesticides, polychlorinated biphenyls (PCBs), and halogenated hydrocarbons. Therefore, cyclodextrins can potentially be used to extract soils contaminated with hazardous compounds. Another advantage of using cyclodextrins is that they are non-toxic, non-hazardous,

biodegradable, water soluble and available commercially at a reasonable cost. Because cyclodextrins are environmentally friendly, there is a potential for their use in the *in situ* remediation of contaminated soils and ground water, without impacting the environment.

Technical Progress and Results: In this study, soils contaminated with various toxic and hazardous organic compounds were extracted with β -cyclodextrin. Initial studies were conducted using natural soil which has been cleaned and spiked with known concentrations of various organic pollutants. The organics tested in the synthetic study essentially contain extractable target compounds listed in the Contract Laboratory Program (CLP) of US EPA's Comprehensive Environmental Response Compensation and Liability Act (CERCLA) or Superfund program, totaling about 91 compounds. This list includes PNAs, PCBs, organochlorine pesticides, halogenated hydrocarbons, organic acids/bases and phenols.

For each group of compounds listed above, 10 g aliquots of spiked soil was extracted with β -cyclodextrin and water. However, for contaminated soil study, only those groups of compounds which showed significant extraction efficiency by β -cyclodextrin were included. This list includes mainly soils contaminated with organochlorine pesticides (two soils collected from a pesticide manufacturing facility in North Eastern USA), PCBs (collected from BNL site) and PNAs (Superfund soil obtained from commercial source as a certified soil).

In the synthetic soil study, β -cyclodextrin was very effective in extracting several toxic and hazardous organic contaminants. For example, the organochlorine pesticides such as aldrin, chlordane, methoxychlor, endrin aldehyde, endosulfan-I, endosulfan-II, heptachlor, and heptachlor epoxide, were

extracted with > 80% efficiency. These results were further confirmed when the experiment was repeated with two real world pesticide soils (low and high concentration levels). The extraction efficiencies for the contaminated soils for the compounds listed above range between 70-100% (Table-1). These compounds are highly chlorinated and structurally diverse compounds with significant toxicity and suspected carcinogenicity.

Similarly, the extraction efficiency of synthetic soil spiked with 100 ppm of PCB - 1248 was 75%. The extraction efficiency of the contaminated soil collected from BNL site was 77% (Table-2). This soil contained ~ 3,900 ppm of PCB-1248. These results show that β -cyclodextrin is an effective extractant and can be used to clean up soils contaminated with organochlorine pesticides and PCBs. In addition, the use of β -cyclodextrin for soil remediation has distinct advantages over surfactant technology in that intractable emulsions are not formed.

Also, lower molecular weight PNA compounds were extracted by β -cyclodextrin in reasonable to excellent yields. For example, compounds such as acenaphthene, acenaphthylene, naphthalene, and pyrene were extracted with > 85 % efficiency. However, the higher molecular weight PNA compounds such as benzo(a)anthracene, benzo(g,h,i)perylene, benzo(a)pyrene etc. were not efficiently extracted by the β -cyclodextrin. The probable reasons for this low extraction efficiency are due to the larger size of the molecules which may not fit into the cavity of cyclodextrin and also due to the low solubility of these compounds in water, thus precluding their availability for complex formation. Further research is needed to improve the extraction efficiency of these compounds. The extraction of contaminated PNA soil is in progress.

Further, the biodegradation of the extracted pollutants in the presence and absence of β -cyclodextrin was investigated. Initial studies were conducted using PNA compounds such as naphthalene and phenanthrene (at 100 ppm each) and the *Pseudomonas putida* bacterium (ATCC # 12633). The rate of biodegradation of naphthalene and phenanthrene was monitored by UV-spectroscopy at 220 and 251 nm, respectively. These results indicate that naphthalene was degraded by the bacterium at the rate of $4.2 \mu\text{mol h}^{-1}$. However, in the presence of β -cyclodextrin, the degradation rate was faster at $9 \mu\text{mol h}^{-1}$. Similarly, the rate of phenanthrene degradation was $1.4 \mu\text{mol h}^{-1}$ by itself, and $3 \mu\text{mol h}^{-1}$ in the presence of cyclodextrin (Figure-1). The addition of β -cyclodextrin accelerated the rate of mineralization of naphthalene and phenanthrene.

In addition, the rate of biodegradation of β -cyclodextrin using a pure culture isolated from the soil collected from BNL site was examined. The pure culture completely mineralized β -cyclodextrin at the rate of $47.3 \mu\text{mol h}^{-1}$.

The advantage of using the *P. putida* for biodegradation of organic pollutants in the presence of β -cyclodextrin is that the bacterium does not degrade cyclodextrin. This means that the β -cyclodextrin can be recycled for further remediation either in *ex situ* or *in situ* mode.

In summary, β -cyclodextrin is efficient in remediating soils contaminated with very

toxic and hazardous organic compounds such as organochlorine pesticides, PCBs and some of the lower molecular weight PNA compounds. These compounds are of significant concern to USEPA and DOE. The advantages of using cyclodextrin for remediation of contaminated soils are that (a) cyclodextrin is an environmentally friendly, non-hazardous, non-toxic and biodegradable compound, (b) no viscous emulsions are formed during extraction, (c) decreases the toxicity of the contaminant by forming the inclusion complex, (d) does not adsorb to the soil, thus minimizing the amount of extractant used, and e) enhanced biodegradation of the contaminants by selected microorganisms.

PAPERS/JOURNALS/PUBLICATIONS:

Patent: A patent application for the extraction of toxic and hazardous organic compounds from soils using cyclodextrin is filed.

FOLLOW-ON FUNDING:

Future funding: Submit a proposal to the Office of Health and Environmental Research (OHER), DOE, in response to Natural and Accelerated Bioremediation Research (NABIR) initiative in FY 1997.

LDRD FUNDING:

FY 1995	\$ 75,555
FY 1996	\$ 73,305

Table- 1: Extraction of organochlorine pesticides from contaminated soils using β -cyclodextrin

<u>Compound</u>	<u>Spiked Soil (a)</u>		<u>Contaminated Soil-1 (b)</u>		<u>Contaminated Soil-1 (b)</u>	
	<u>Initial</u> (ug/g)	<u>% removal</u>	<u>Initial</u> (ug/g)	<u>% removal</u>	<u>Initial</u> (ug/g)	<u>% removal</u>
aldrin	100	100	NP	NA	106	90
alpha-BHC	100	80	0.3	44	173	68
beta-BHC	100	100	0.6	92	12	54
delta-BHC	100	60	2.8	89	35	67
gamma-BHC	100	94	0.4	45	227	65
alpha-chlordane	100	92	8.6	86	39	74
gamma-chlordane	100	90	14.3	86	46	74
4,4'-DDD	100	65	21.4	30	85	15
4,4'-DDE	100	18	10.3	61	26	28
4,4'-DDT	100	61	155	44	392	20
dieldrin	100	100	10.6	100	69	100
endosulfan-I	100	100	NP	NA	NP	NA
endosulfan-II	100	65	NP	NA	NP	NA
endosulfan sulfate	100	61	NP	NA	NP	NA
endrin	100	100	NP	NA	29	26
endrin aldehyde	100	99	6.7	70	NP	NA
endrin ketone	100	84	NP	NA	NP	NA
heptachlor	100	99	9.7	97	29	86
heptachlor epoxide	100	99	NP	NA	2.0	85
methoxychlor	100	84	NP	NA	24	100

Table- 2: Extraction of polychlorinated biphenyls from contaminated soil using β -cyclodextrin

<u>Compound</u>	<u>Spiked Soil (a)</u>		<u>Contaminated Soil-1(c)</u>	
	<u>Initial</u> (ug/g)	<u>% removal</u>	<u>Initial</u> (ug/g)	<u>% removal</u>
PCB-1248	100	75	3,900	77

(a) synthetic soil prepared by spiking a clean soil with certified Supelco standard.

NP= not present in the sample.
NA= not available

(b) naturally contaminated soils obtained from a pesticide manufacturing facility in NE United States.

(c) a naturally contaminated soil obtained from BNL site.

NOTE: The extraction efficiencies of PNA compounds, phenols, chlorinated hydrocarbons, acids/bases, which are part of the EPA CLP Extractable Target Compound List of compounds, for the spiked soil study not included in this report are included in the LDRD Report submitted to DOE in FY 1995 (Ref: 95-44).

Figure 1. Degradation of naphthalene and phenanthrene by *P. putida*

Positron Emission Magnetic Resonance Imaging (PEMRI)

*Charles S. Springer, Jr. and
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96-06

PROJECT DESCRIPTION:

Three of the most powerful medical imaging techniques in use today are positron emission tomography (PET), single photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI). In a major new initiative, the Department of Energy (DOE) and Brookhaven National Laboratory (BNL) have recently moved to incorporate SPECT and MRI Laboratories with the world-renowned PET Laboratory at BNL. The entity encompassing these is the *Brookhaven Center for Imaging and Neuroscience* (BCIN). Early this year, a new SPECT Laboratory was set up in the Medical Building. A new High-Field MRI Laboratory Building has just been completed by BNL, housing a new MRI instrument purchased by DOE with help from NIH, which features a magnet with a field strength of 4 Tesla. This is the largest field strength used for humans, and there are only seven such instruments in the world. The MRI Lab achieved its first human images in June, and has spent the Summer in acceptance testing and fine-tuning the complex NMR system. A next-generation PET instrument will be installed in the PET Lab early next year. The PET Building is diagonally across an intersection from the MRI Building.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: A charter mission of BCIN is to develop synergistic combinations of these imaging techniques. We are going about this

in the most fundamental way possible, and this requires understanding exactly what information each kind of image contains. A significant fact is that the major strengths and weaknesses of PET and SPECT are rather complementary to those of MRI. We will illustrate this with PET, but similar comments can also be made with regard to SPECT.

The PET technique has the incomparable strength of being able to detect tiny (sub-nanomolar) concentrations of any of the vast array of bioactive compounds that clever chemists can label with the PET isotopes of nature. On the other hand, metabolic MRI is restricted to the detection of only a few of the handful of metabolic compounds that have concentrations greater than one millimolar. The spatial and temporal resolution of PET, however, is rather poor (no better than a few mm, and minutes, respectively). In sharp distinction, anatomical MR images made from the strong, ubiquitous $^1\text{H}_2\text{O}$ signal (the $[^1\text{H}]$ in tissue water is *ca.* 100 molar) can have very favorable spatial and temporal resolution (sub-mm, and seconds). At a slight sacrifice of spatial resolution, ultra-fast MR images can even be obtained in less than 100 ms.

Approach: We have begun testing a new approach involving the complete convolution of the data obtained from a PET scan with the data from an anatomical MRI scan of the same brain slice of the same human subject. The PET Lab archives contain image data from many subjects. Figure 1 depicts an archive PET image of a transverse slice of the brain at the level of the *centrum semiovale* (near the top of the brain) as viewed from an inferior perspective (*i.e.*, while the top of the image is the front of the brain, the right side of the image is the left side of the brain). The image was produced after injection of the tracer ^{18}F -labeled fluorodeoxyglucose (FDG), and has a nominal in-plane resolution of $(6.5 \text{ mm})^2$, with a slice thickness of 6.7 mm.

Figure 1.

With the convenient configuration of the PET and MRI Laboratories of BCIN, the coordination of the acquisition of such data with that of MRI data from the same subject will now be quite straight-forward. However, in order to avoid a delay in this project while the 4T BNL MRI instrument was becoming operational, we began analysis with MRI data from the Department of Radiology at the University at Stony Brook (USB), obtained with a clinical instrument having a lower field strength (1.5 T). Thus, Figure 2 shows an MR image of the same subject as in Figure 1, and the same slice and orientation. It has a nominal in-plane resolution of $(0.9 \text{ mm})^2$.

Figure 2.

Although this image does not have particularly high contrast, it was obtained with an RF pulse sequence that rendered the depiction of the cortical gray matter somewhat brighter than that of the deeper white matter. Thus, there is some gray/white matter contrast, and some brain anatomical features are apparent in the image.

It is important to note that the image data of Figures 1 and 2 have already been centered, oriented, and scaled such that they could be exactly overlaid. This was accomplished using Dr. Levy's GALAXY approach.¹

Technical Progress and Results: As outlined in the original proposal, the new method used here involves combining the data from the two experiments at a fundamental stage of image processing. Specifically, the so-called k-space images are convolved. These are the Fourier transforms of the real space images, which are seen in Figures 1 and 2. A k-space image is a kind of interferogram that exhibits only diffraction-type patterns, not the objects of real space. Such transformations were accomplished for the image data of Figures 1 and 2. When the PET and MRI k-space images are convolved, the PET inculcates metabolic information in the low spatial frequency components.² The MRI, however, supplies the high spatial frequency components not present in the PET data. The convolution is carried out following the general principles underlying the Constrained Reconstruction Methods.³ After the appropriate convolution of the PET and MRI k-space images, a back Fourier transformation produces a *true hybrid* real space image that contains information from both basis images. We call it a *positron emission magnetic resonance image* (PEMRI) and, in principle, it can present PET tracer mapping with a spatial resolution approaching that of MRI. As stated above, the latter is (generally speaking) about an order of magnitude greater

than the spatial resolution of PET. The first such image is depicted in Figure 3. It shows an

Figure 3.

encouraging increase in detail over the PET image seen in Figure 1. That the increase is more subtle than one might expect is due mostly to the lack of significant contrast in the MR image. Much higher contrast (conspicuity) is possible with MRI. Figure 4 depicts one of the earliest images obtained with our new 4T instrument at BNL by Dr. J-H. Lee. It is of a transverse slice

Figure 4.

of a different subject, and at a slightly different level of the brain. It has a nominal in-plane resolution of $(1.56 \text{ mm})^2$, with a slice thickness of 5 mm. Since this image was

obtained as part of an evaluation of a new RF pulse sequence intended for other purposes, its spatial resolution was intentionally only modest. We have already obtained other images with in-plane resolutions of $0.39 \text{ mm} \times 0.48 \text{ mm}$ using our new instrument. The image shown in Figure 4 does, however, exhibit excellent gray/white matter contrast. If we had an FDG PET image of the same slice of the same subject, the PEMRI picture would show much higher conspicuity than that in Figure 3.

Thus, PEMRI represents the synergistic enhancement of *both* the PET and MRI images. It is possible that it might even permanently alter the practice of PET. The SPECT analog will be called SPEMRI (single photon emission magnetic resonance image). Of course, this approach can be applied to the combination of ultrasound, or x-ray (CAT scan) image information with MRI information (USOMRI, CAMRI ?). The analogous data from any pair of imaging techniques can be convolved according to these fundamental principles. The PEMRI method will also be useful for the data set pairs acquired from a combination PET/MRI instrument. Though we are not convinced of the wisdom of the latter approach, at least one group is involved in constructing and testing a prototype device for small animal models.

It is most important, however, that one be concerned with the assumptions that are involved with such a mathematical combination of these data. In this regard, it helps to think qualitatively about what information an image contains. The interpretation of a PET (or SPECT) image is reasonably straightforward. It depicts the spatial distribution of a radiotracer in the tissue. The brighter the picture element (pixel), the greater the number of tracer molecules in the volume element (voxel) represented by that pixel. What one would

like is for the MR image to simply provide the tissue compartmental boundaries, with high definition, in order to aid the PET intensity to distribute itself with higher spatial resolution. A traditional MR image, however, is more subtle. If one makes an image where pixel brightness simply represents the number of water molecules in the voxel, there is little contrast - because this number (the so-called spin density) is rather uniform in all of the tissue. We have such an image of the same slice as seen in Figure 4. Contrast in an MR image (such as in Figure 4) is usually produced by *reducing* the brightness in a pixel from the spin density value, by some factor that is a function of a relaxation time of the water NMR signal from the voxel represented by that pixel. This is because water signals from different tissue regions do have different relaxation times. Thus, pixel intensity in any traditional MR image involves spin density and relaxation time information combined in a way that cannot be easily, if at all, separated.

Our new type of *relaxographic* MR images⁴ can provide quantitative spin density information along with high contrast dictated by the relaxation time variation. Thus, the spin density can be used to measure the spatial extent of a compartment since, as implied above, it is a good metric of volume. We have used relaxographic imaging principles to produce "naturally" segmented images.⁵ Examples of these are shown in Figures 5 and 6, which depict the same slice, with the same resolution, and from the same subject, as in Figure 4. These were produced by Ms. I. Palyka and Mr. X. Li. In Figure 5, for example, one sees only the white matter water, and with complete contrast. Figure 6 depicts only the gray matter water, again with complete conspicuity. As might be expected from the above, these two images are almost completely complementary to each other.

Figure 5.

Figure 6.

These images were obtained with BNL 4T data. Dr. Levy has also devised another method for segmenting MR images, which relies completely on post-acquisition image processing principles.

Such segmented MR images will provide a very important test for the PEMRI approach. The tracer FDG is known to concentrate quite selectively in the gray matter.⁶ Thus, if we convolve the k-space image of an FDG PET map, such as that seen in Figure 1, with that of an MR gray matter water map, such as that seen in Figure 6, of the same slice of the same subject, we should obtain a PEMRI map with the spectacular (for PET) resolution seen in Figure 6. On the other hand, if we use an image analogous to the white matter water

map of Figure 5 as the MR mask for the PEMRI process, the PET and MRI data would be in severe conflict. Thus, the PEMRI map should have much worse resolution than the PET image. This will demonstrate clearly and decisively that one cannot simply apply the PEMRI method indiscriminately. We will try to develop a mathematical criterion of compatibility of the PET and MRI data.

PAPERS/JOURNALS/PUBLICATIONS:

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³Z-P. Liang, F. E. Boada, R. T. Constable, E. M. Haacke, P. C. Lauterbur, and M. R. Smith, *Revs. Magn. Reson. Med.* 4 67-185 (1992).

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⁶J. C. Mazziotta, and M. E. Phelps, Chapt. 11 in *Positron Emission Tomography and Autoradiography: Principles and Applications for the Brain and Heart*, Ed. by M. Phelps, J. Mazziotta, and H. Schelbert, Raven Press, NY (1986), pp. 493-579.

A manuscript describing the first results will be prepared.

LDRD FUNDING:

FY 1996	\$ 100,208
FY 1997 (est.)	\$ 170,000

Note: This project involves animal vertebrates or human subjects.

Coherent Synchrotron Radiation Experiment

James Murphy

96-10

Eric Blum

Richard Heese

John Keane and

Samuel Krinsky

PROJECT DESCRIPTION:

The broadband nature of synchrotron radiation facilitates scientific studies from the hard x-ray regime to the infra-red portion of the electromagnetic spectrum. At present the synchrotron radiation in use at all existing light source facilities is "incoherent," meaning that the intensity of radiation is directly proportional to the number of electrons in a bunch. If the electron bunch length σ can be made short enough there is the possibility of "coherent" emission where the radiation intensity scales as the square of the number of particles in an electron bunch (N^2) for wavelengths $\lambda \geq \sigma\pi$. At present it is impossible to achieve short enough bunches for the generation of coherent x-rays, but it is possible to produce sub-millimeter electron bunches to generate coherent far infra-red radiation. Far infra-red coherent synchrotron radiation has been experimentally observed at several labs using the electron beam from a linac and a bending magnet in a transport line. In this LDRD project, we propose to carry out research and development to lay the foundation for an experiment to produce the first coherent far infra-red synchrotron radiation in an electron storage ring.

The experiment [1] we are considering would make use of the existing XLS Phase I storage ring and the 200 MeV electron linac injector at the Source Development Lab. To produce the sub-millimeter electron bunches

in the XLS ring we could use a high voltage, superconducting 1.5 GHz RF cavity. The combination of high voltage and high frequency would compress the bunch to $\sigma \approx 0.3$ mm, providing for coherent synchrotron radiation in the far infrared, $\lambda \geq 1$ mm. In a second phase of the experiment, we plan to reduce the momentum compaction of the ring by a factor of four, shrinking the bunch length by another factor of two, yielding coherent synchrotron radiation at 500 microns with an intensity several orders of magnitude beyond what is presently available on the infra-red beam lines at the NSLS. These electron bunch lengths are more than an order of magnitude smaller than in any existing electron storage ring. As such the experiment provides for exciting accelerator physics and a unique intense far infra-red radiation source, utilizing a wealth of existing hardware at the NSLS, developed as part of the SXLS project.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: The key to success of the experiment is the design and construction of the 1.5 GHz superconducting RF cavity system. It is also important to assess the effects of short bunches in the storage ring. The LDRD grant money was used to develop a model of the RF cavity in order to assess the issues of input power coupling, damping of higher order modes, frequency tuner development, the effects of reactive beam loading and cryostat design. Theoretical studies were carried out to determine the electron beam stability for extremely short bunches. Consideration was given to the impedance of the storage ring components and the impedance associated with the emission of the synchrotron radiation itself. This is a new regime for storage ring operation and as such requires a thorough investigation of the electron beam intensity limits. Finally, the operation of the XLS ring with a reduced

momentum compaction was analyzed with the goal of producing 500 μm coherent synchrotron radiation.

Approach: A collaboration with the Thomas Jefferson National Accelerator Facility (formerly CEBAF) was established with the goal of TJNAF developing a conceptual design of the electrical, mechanical and cryogenic aspects of the superconducting RF cavity. Such an arrangement gave us access to the wealth of experience at TJNAF in the area of superconducting RF and fostered inter-laboratory collaboration. To expedite the design of the RF cavity, the frequency was taken to be 1.5 GHz which conforms to the original design of the CEBAF cavities. Theoretical work on the electron beam wakefields and stability were performed by the NSLS accelerator R&D group. Studies of a storage ring with a reduced momentum compaction were carried out on the existing NSLS VUV ring.

Technical Progress and Results: The conceptual design of a 3 cell, 1.5 GHz, 3 MV superconducting RF cavity based on the original CEBAF cavity has been completed by TJNAF [2]. This compressive study addressed the issues of compactness necessary to fit the cavity in the small XLS storage ring, the modification of the CEBAF cavity from 5 cells to 3 cells, the higher order mode analysis and its impact on cryostat design and the required refrigeration. In addition, the RF power requirements and control systems were assessed. To facilitate future rapid realization of the cavity, cost and schedule estimates were also delivered.

The short bunches in the ring are produced by the high frequency/voltage RF cavity, but it is important to assess the impact collective effects have on the stability of the electron bunches. To this end, extensive analytical and numerical work was performed by the NSLS

accelerator R&D group to explore the longitudinal wakefield due to synchrotron radiation. Novel results were obtained on the wakefield for an electron circulating in free space and midway between infinite conducting parallel plates [3]. Using this wakefield the effects of longitudinal potential well distortion on the equilibrium electron bunch distribution were analyzed [4]. One intriguing possibility is that the sharpening of the leading edge of the longitudinal density profile may extend the wavelength region in which coherent emission occurs from 1 mm down to 300 microns, even without reducing the momentum compaction. Work continues to examine the stability of the short bunches in the ring.

To explore the operation of a storage ring with a reduced momentum compaction, studies were carried out on the existing NSLS VUV ring. It was shown that the momentum compaction could be reduced by at least an order of magnitude. In addition, operation of the ring with a negative momentum compaction and no sextupoles was also successfully achieved.

The coherent synchrotron radiation experiment is poised to pursue funding for the manufacture of the superconducting RF cavity and assembly of the XLS storage ring.

PAPERS/JOURNALS/PUBLICATIONS:

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[2] "Final Report on the Design Study of an RF Bunching System for BNL by TJNAF," report received (10/96).

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submitted to **Particle Accelerators** (4/96).

LDRD FUNDING:

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K. Bane, S. Krinsky, and J.B. Murphy, **AIP
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FY 1996

\$49,799

In-Vacuum Undulator (IVUN) for the NSLS X-ray Ring

P.M. Stefan

96-11

S. Krinsky

D.R. Lynch and

G. Rakowsky

PROJECT DESCRIPTION:

The development of in-vacuum, short-period undulator insertion devices may be important to the future role of the NSLS within the synchrotron radiation community. In a number of experimental areas, such insertion devices would position the NSLS at the state-of-the-art as a radiation source, even against the third generation storage rings. Nevertheless, the realization of such a device requires an extension of existing technology. Preliminary studies addressing key issues for a prototype in-vacuum undulator (IVUN) for the X13 R&D insertion straight section are being conducted.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: The NSLS Prototype Small-Gap Undulator (PSGU) project has successfully obtained small electron beam apertures (<4 mm) with long beam lifetimes in the X13 R&D insertion straight section, and produced intense synchrotron radiation with its 16 mm-period undulator. The PSGU incorporates a variable-aperture vacuum chamber, and a separate magnet drive with the undulator arrays, which operates in air. As a result of this construction, the undulator magnet gap is always at least 3 mm greater than the electron beam aperture. A logical extension beyond the PSGU is to eliminate the variable-aperture vacuum chamber and place the undulator

magnet arrays directly in the accelerator vacuum: an in-vacuum undulator, IVUN. Challenges associated with the IVUN approach include: 1) undulator array construction adapted to ultra-high vacuum (UHV) requirements, 2) high sensitivity magnetic measurements for construction and verification of the small-gap magnet arrays, 3) radiation damage to essentially unshielded NdFeB magnets located near the stored electron beam, 4) mechanical systems to support, align, and drive the in-vacuum arrays. Proposing and testing technical solutions to these challenges is the purpose of this project.

Successful realization of a prototype IVUN device in the NSLS X-ray Ring would make possible the development of significant new x-ray sources for the NSLS Users. Each of the two NSLS X-ray Ring RF straight sections could be modified to accommodate in-vacuum undulators, which would bring the total number of insertion device ports to 7 on the X-ray Ring.

Approach: For many of the challenges posed by an IVUN device, workable technical solutions can be evaluated through the construction and testing of simple mock-ups and prototypes, or in some cases, through analytical or finite-element models.

Technical Progress and Results: In parallel with this project, a collaboration with colleagues at the Japanese SPring-8 project has been established for the construction of IVUN magnet arrays. Their expertise and previous success with in-vacuum undulators answers many of the IVUN questions related to UHV compatibility. However, two areas associated with the attainment of good UHV are proper bake-out and in-situ glow-discharge cleaning. To obtain thorough magnet array heating, while avoiding over-temperature excursions, a scheme to flow

heated, de-ionized water through the undulator array cooling channels has been proposed. A portable water heater with controls has been designed and will be built to test this approach.

In-situ glow-discharge cleaning was used in PSGU to reduce photon-stimulated gas desorption in the newly-installed device. Similar provisions are being made for IVUN, but two uncertainties arise. In IVUN, glow-discharge cleaning will take place in the presence of the undulator magnetic fields, unlike PSGU, in which the magnets were removed for bake-out and glow-discharge cleaning. In addition, the maximum electron beam aperture is smaller in IVUN than in PSGU. These factors may lead to "obstruction" of the glow discharge, in which the IVUN components immediately surrounding the electron beam location will not receive the full ion dose desired. A small prototype chamber has been constructed to test these effects. It incorporates 0.5 mm thick stainless steel "bread pans" to create the small-gap region and to permit magnets to be installed on the air side to simulate the IVUN magnet arrays. Using this prototype, glow discharge conditions which yield effective cleaning will be developed.

As part of this project, three areas are being pursued for magnetic measurements of small-gap devices: pulsed-wire techniques, moving wire integration, and small Hall probes. In the pulsed-wire technique, first developed at Los Alamos National Lab, a thin, tightly-stretched wire ($\sim \phi 125 \mu\text{m}$) is located on the electron beam axis of the undulator. A current pulse sent down the wire interacts with the undulator magnetic fields to produce a transverse displacement train on the wire. This displacement train travels down the wire where it is detected by two laser-diode/photo-sensor stations. By choice of the excitation pulse length, either the first or second integral

of the magnetic field is obtained directly, with the effect of each magnetic pole clearly displayed. The major benefits of the technique are its speed (in principle, a few milliseconds to collect a data set; in practice, some signal averaging is necessary), compatibility with very small magnet gaps, and ability to localize defects within the array. A setup has been constructed and is ready for initial tests.

The moving wire integration method uses a flexible, multi-loop integrating coil. A section of multi-conductor Litz wire ($< \phi 1.5 \text{ mm}$) is mounted between motorized stages at either end of the undulator and forms one side of the multi-loop coil. Using the stages, the wire can be translated in and out of the undulator field. The voltage induced in the loop as it encloses magnetic field is recorded in a sensitive integrator. Through a series of translations, which sequentially position the wire within the undulator and subsequently remove it to a field-free region, multipole fields, integrated over the length of the undulator can be obtained. The small diameter of the Litz wire makes this technique applicable to small magnet gaps. All the hardware has been prepared to perform moving wire measurements, only the programming remains to be done.

Two types of Hall probes have been investigated for IVUN field mapping. One is a commercial probe. It has built-in thermistors and comes with factory calibration curves for the necessary temperature compensation. While not applicable to very small magnet gaps, this probe may be usable at the IVUN nominal design gap of 3 mm. The second probe investigated is a simple Hall element, provided in a small surface-mount package (1.7 mm x 1.9 mm x 0.9 mm). The sensitive area of the probe is $125 \mu\text{m} \times 125 \mu\text{m}$. Breadboard tests have already been made with these sensors.

As part of this project, several aspects of the IVUN mechanical systems were examined using finite-element analysis and simple prototypes. In the PSGU, an unexpected deflection of the magnet drive system was found when the magnet gap was small (large attractive force between the magnet arrays). Although a similar concept has been adopted for the IVUN magnet drive, the proposed design was subjected to a finite element stress analysis to predict the worst-case deflections under load. The results immediately identified the main welded framework of the drive as a major source of deflection. This was unanticipated and explained much of the deflection seen in the PSGU. Consequently, the IVUN framework design was significantly modified to stiffen it. In addition, box-beam assemblies in the drive were also examined by finite-element analysis, and significant modifications were made to the initial designs to reduce deflection under load.

A finite element *thermal* analysis of the in-vacuum magnet beams was also conducted. When operated in a storage ring, heat is deposited in the undulator arrays through the action of the stored electron beam on the resistive wall impedance. Without active cooling of the magnet arrays, these structures will become very hot, not because the deposited power is great (≤ 20 W), but because the structures are suspended in vacuum and consequently are well-insulated against convective or conductive heat transfer. A 2-d finite-element model was made to evaluate the effectiveness of the proposed cooling design, which used water channels milled in the main aluminum magnet support

beams. A temperature rise of only a few °C was predicted under worst-case conditions.

The vacuum integrity of the main flanged connection between the aluminum magnet beams and the magnet drive system was tested with simple prototypes. Stainless steel conflat-type flanges are commonly used for UHV connections. However, in the proposed IVUN design, an aluminum conflat-type flange would be used on the aluminum main magnet beam to avoid stainless-steel/aluminum transition material. It would be bolted to a mating stainless-steel flange on the magnet drive. Simple prototype pieces were made to test 3 aspects of this connection: 1) weld-ability of aluminum conflat-type flanges of two different alloys (Al-6061-T6 and Al-2219-T87) to similar and dissimilar aluminum alloys, 2) reliability of the flanged connection under repeated bake-out to 150°C, 3) ability of this flanged connection to remain leak tight under a tensile load of 9 kN (2000 lbf), the maximum magnetic load. Four test flange assemblies were fabricated. No significant problems were experienced in the welding. All the connections to stainless-steel conflat flanges remained leak-tight after multiple 150°C bake-outs. Connections were also leak-tight at 150°C. A fixture using Belleville washers was fabricated to apply the 9 kN load while the test flange-pair was mounted on the leak detector. No leak developed during or after several applications of the load.

LDRD FUNDING:

FY 1996	\$100,118
FY 1997 (est.)	\$100,000

Spin Polarized Coincidence Spectroscopies

Peter D. Johnson

96-16

PROJECT DESCRIPTION:

Spin-polarized core level photoemission offers the possibility of site-specific magnetic information. Soft x-ray fluorescence is a technique that is again site-specific, but now offers the possibility of studying the valence bands. Thus, in combining the two techniques, the present project hopes to develop new methods of obtaining site-specific spin-resolved valence band information and the related spin moments in systems such as ferromagnetic alloys and compounds grown in thin film form. The work relies on the use of a new high resolution electron analyzer acquired at the end of fiscal 1995 and is based at beamline X1B at the NSLS.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: Site specific valence band information is difficult to obtain in alloys and compounds. However, techniques that rely on the initial excitation of a core level offer the possibility of obtaining such information. The main goal of this project is the development of a coincident technique that will allow the measurement of site-specific and spin dependent valence band information. It is hoped that the techniques will be used to study thin film ferromagnetic alloys. Through the use of controlled epitaxial growth on different substrates, we hope to study unique phases of these materials not available in the bulk. By varying the growth conditions it will be possible to study not only ordered phases, but also the effects of order-disorder

transitions. Indeed, growth on different substrates may be viewed as a way of applying pressure to the system so that a whole range of magneto-volume effects may be studied. Such information is difficult to come by using any existing methods. We also hope to study organic superconductors and oxide thin films displaying giant or colossal magneto-resistance.

Approach: Spin polarized core level photoemission does not in itself provide valence band information, but the radiative decay of the core hole does involve electrons from the valence band. Further, the electrons involved in the radiative decay must carry the same spin as the core hole. Thus, labeling the spin of the photoemitted core electron is equivalent to labeling the spin of the valence electron. By measuring the energy of the radiated photon in coincidence with the spin polarization of the photoemitted core electron, we hope to be able to measure the spin resolved valence bands on the site from which the initial core electron was emitted.

Technical Progress and Results: During the last year, the new Scienta hemispherical electron analyzer has been coupled to the experimental chamber and commissioning begun. Vacuum and magnetic field problems can be more critical with a large instrument of this type. However, considerable progress in these two areas has been made. New "user friendly" software has also been developed to drive the analyzer.

A spin polarimeter has been designed at Brookhaven and manufactured at Boston University. A measure of the efficiency of a polarimeter is given by the Figure of Merit (FOM) defined as

$$FOM = S^2 \frac{I}{I_0}$$

where S is the Sherman function and I/I_0 gives the scattered intensity I normalized to the incident current I_0 . The Sherman function represents the contrast measured in the two scattering channels of the spin polarimeter for an incident 100% spin polarized beam.

The new spin polarimeter, based on earlier designs of the Mott variety, uses electron optics in the scattering channels to increase the collected intensity and optimize the FOM. This polarimeter, shown in the figure, is now being assembled and will be tested in the near future.

The proposed experiment requires the initial excitation of more deeply bound core levels in the vicinity of 600-800 eV binding energy. The blazed grating in beamline X1B monochromator has, therefore, been successfully replaced with a laminar holographically ruled spherical grating. While the two gratings have the same line density, 800 lines/mm, the laminar grating has much greater efficiency at the higher photon energies.

Mott Spin Polarimeter

Scattering energy : 25 KeV

Expected efficiency $\sim 4.2 \times 10^{-4}$

LDRD FUNDING:

FY 1996	\$78,999
FY 1997 (est.)	\$82,000

An Evaluation of the WSR-88D for the Remote Sensing of Cloud Properties

*Mark A. Miller and
Peter Daum*

96-19

PROJECT DESCRIPTION:

The new National Weather Service WSR-88D radars, deployed at 150 sites in the United States and 19 sites abroad, provide unprecedented areal radar coverage. Each radar can perform volume scans measuring reflectivity, radial velocity, and spectral width over an area exceeding 280,000 km² every 5-10 minutes. Calculations suggest that it is possible to estimate the fractional coverage, geometry, and evolution of non-precipitating clouds over a significant subset of this measurement volume, which makes the WSR-88D a potentially cost effective tool for cloud research. Potential applications of this cloud sensing technique range from fundamental research on cloud development to improved temperature and cloudiness forecasts.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: Clouds cover a very large fraction of the earth's surface and have a large effect on the earth's shortwave radiation budget because of their high albedo. In contrast, clouds have varying effects on the longwave budget depending on their location in the troposphere; high clouds strongly influence the outgoing longwave flux, while low clouds have minimal influence since their cloud top temperatures are only slightly lower than the surface temperature. Thus, the net thermal response of the earth's surface to overlying clouds is dependent upon cloud-type: high clouds warm the surface and low clouds cool

it. Because the characteristics of cloud fields are difficult to quantify, the impact of cloudiness variations on the earth's radiation budget is a major unsolved problem in atmospheric research. Consequently, clouds are very difficult to represent in short term forecast models and in Global Climate Models (GCM), which are used to estimate the future consequences of fossil fuel consumption and to evaluate future energy use scenarios.

Sophisticated short-wavelength cloud radars (<9 mm) have been deployed during the past decade to help provide a database from which improved cloud parameterizations can be formulated and tested. Unfortunately, these specialized radars probe a limited area (~400 km²), are extremely expensive to construct and to operate, and are available only for temporary deployments. Hence, there is a basic need for a reliable, continuously operating, cost-effective measurement system that can quantify cloud structure over a relatively large spatial domain.

Approach: Cloud droplets present a relatively small backscattering cross-section to radars such as the WSR-88D, with its 10 cm wavelength. Even with advanced signal processing, clouds reside at the edge of detectability and are less likely to be detected as their distance from the radar increases. Consequently, it is necessary to carefully consider the range- and elevation-dependent threshold of detection of the WSR-88D to insure that clouds in the sampled volume are both detectable and fully resolved. The cloud detection capabilities of the radar can be quantified using a combination of theoretical calculations and measurements, which constitutes the first phase of this project. The second phase of this project entails the development of cloud retrieval algorithms that interface with existing WSR-88D data analysis packages, and evaluation of them by

comparing with measurements from other systems.

Technical Progress and Results: The effective reflectivity of clouds is dependent on several factors, including the phase of the water that composes the cloud particles. Only liquid droplets are considered in the calculations that follow because their backscattering cross-section is a well known function of droplet size. A range of effective reflectivities that includes typical non-precipitating liquid clouds is -15 to -30 dBZ, and the latter value is used as a reference point in the remainder of this paper since it represents the weakest echoes.

The capability of the WSR-88D radar to remotely sense clouds is quantified by its range-dependent Minimum Detectable Signal (MDS). Physically, the MDS is the theoretical threshold of detection, which requires that the signal-to-noise ratio at the output of the receiver be greater than unity. Although the radar calibration coefficient (radar constant), receiver noise characteristics, and signal averaging must be considered in the computation of the MDS, only signal averaging is not constrained by the radar hardware and can be easily modified. In theory, it is possible to detect any signal, no matter how low the signal-to-noise ratio, by averaging more samples. In practice, however, it is usually not possible to average an unlimited number of samples because the processing time required may exceed the maximum sampling time necessary to characterize the meteorological process under study. With regard to the WSR-88D radar, the operator has limited flexibility to adjust the number of sample averages, which is governed by the pulse repetition frequency (PRF). Fortunately, the standard PRFs used in the WSR-88D allow cloud detection in many circumstances.

The WSR-88D can transmit two pulse widths, but we will consider only the 4.57 μ s pulse width because it provides maximum radar sensitivity. Using this pulse, there are two modes of operation that are distinguished by different PRFs and scanning strategies: the surveillance mode and Doppler mode. Figure 1 shows how the MDS varies as a function of the number of signal averages, n (a surrogate for PRF) for the 4.57 μ s pulse when the WSR-88D is operated in these two modes. This figure shows that the maximum sensitivity is obtained when the radar is operated in the Doppler mode, which allows detection of clouds (-30 dBZ) to a maximum range of ~40 km along the beam.

While the MDS of the WSR-88D is fundamental to cloud detection, an equally important issue is the scanning strategy, or volume coverage pattern (VCP). The VCP is the algorithm that controls the elevation and azimuth angles of the antenna, as well as its rotation rate. For research grade radars, the VCP can be manipulated as desired, but for operational systems such as the WSR-88D, VCPs are predetermined and not easily modified. Thus, it is necessary to analyze how the available VCP patterns used in the system affect the ability of the system to detect cloudstructure.

Figure 1. Minimum Detectable Signal versus range and number of return pulses averaged for the 4.57 μ s pulse.

At present, there are five VCPs used in the routine operation of WSR-88D. In this

summary, only one of the five VCPs is considered. In this VCP, designated #31, a complete azimuth scan encompassing 360° is performed at each of five elevation angles ranging from 0.5° to 4.5° . The relationship between each of these elevation angles and the spatial characteristics of the MDS is shown in Figure 2. As illustrated, the $4.57 \mu\text{s}$ pulse when transmitted at 4.5° elevation cannot sample heights less than 4 km at ranges greater than $\sim 26 \text{ km}$, but virtually all clouds are detected. In contrast, at the 0.5° elevation angle, all clouds are detected to a range of 40 km , although only fogs and extremely low stratus can exist at the sampled heights; in addition, there are potential problems with ground clutter at this 0.5° elevation angle that are not problematic at higher elevation angles. Therefore, there are important trade-offs between the selected VCP and the MDS characteristics that may constrain the radar configuration used to sample a particular cloud type.

The initial experiment to determine the validity of the calculations discussed above was conducted on February 23, 1996 and selected results are shown in Plate 1. This experiment was performed during a synoptic weather situation characterized by stratocumulus clouds whose tops exceeded 3 km , as estimated from soundings in the region. The elevation angle for this test was chosen as 1.5° to insure that the beam did not exit cloud top before the maximum detectable range for signals on the order of -24 to -28 dBZ (the observed reflectivity in these clouds) was obtained. Thus, a situation was produced in which the backscattered energy from the target cloud droplets fell below the minimum detectable signal threshold of the radar receiver before exiting cloud top. In other words, the cloud echoes were lost in the receiver noise, even though the sampled volume still contained cloud droplets. Using the $4.57 \mu\text{s}$ pulse width, Plate 1 shows that the

signal from the target cloud and drizzle droplets became undetectable at a range of approximately $38\text{--}49 \text{ km}$. The radar calibration of the WSR-88D is electronically monitored and it is known that the effective reflectivities are 2.75 dBZ less than the value reported on Plate 1 (-27 to -31 dBZ). When this calibration is considered, this experiment (as well as several additional experiments that gave similar results) suggests that the MDS function for the WSR-88D is well represented by the curves in Figures 1-2.

Figure 2. The Minimum Detectable Signal of the $4.57 \mu\text{s}$ pulse with $n=63$ versus range, height, and elevation angle.

We have confirmed by both theoretical calculation and several experiments that the WSR-88D can be used to detect the structural elements of boundary layer clouds (cloud top height, cloud fractional coverage, and reflectivity), although careful consideration must be given to the MDS and VCP. Moreover, boundary layer cloud retrievals are possible despite the technical constraints imposed on the radar by its operational charter. For example, using VCP #31, we have determined that the elements of a cloud deck with a base at 800 m , a top at 1000 m , and an effective reflectivity of -30 dBZ can be retrieved over an area of over 616 km^2 , while one with a base at 1600 m , a top at 2000 m , and the same effective reflectivity can be retrieved over an area of over 2460 km^2 . In these examples, the domain over which the

cloud structure can be quantified has a washer-like shape with a data-void region inside the 7 and 12 km radials, respectively. In general, the area over which the cloud structure can be sampled depends on the structural characteristics of the cloud field and the size of the constituent cloud droplets, and it is likely that marine clouds may be sampled over a larger area than continental clouds. Remote sensing of high level clouds (base height >4 km) with the WSR-88D is possible using the higher scan angles of the current operational VCPs.

The results of the first phase of this study are very encouraging, and we are currently developing cloud retrieval algorithms based on low level output from the WSR-88D (Level 2 data). Algorithm development and evaluation is being done in collaboration with the Pennsylvania State University and the Brookhaven National Laboratory Office of the National Weather Service. In the former case, measurements from a Eulerian cloud sensing system comprised of surface-based remote sensors are being used to validate algorithms. In the latter case, the National Weather Service is collaborating with us to develop a specialized algorithm for the detection of cloud top height over a large area and to evaluate the results of our research for potential application to real-time forecasting. We are attempting to assess how the cloud retrieval algorithms may be implemented in programs designed to improve cloud parameterizations in GCMs.

PAPERS/JOURNALS/PUBLICATIONS:

A description of this work appears in *A Review of Research and Development Activity Related to WSR-88D Algorithms* (Brandes, 1996) and during the coming year, manuscripts will be submitted to the *Bulletin of the American Meteorological Society*, the *Journal of Oceanic and Atmospheric*

Technology, and a special issue of *Weather and Forecasting*. A presentation describing this work was given at the 15th Conference on Weather Analysis and Forecasting and a paper will be submitted to the 28th Conference on Radar Meteorology. Research completed as a precursor to this work was presented at the 12th International Conference on Clouds and Precipitation and is described in a manuscript currently undergoing internal review.

FOLLOW-ON FUNDING:

A proposal for follow-up funding will be submitted to the Department of Energy's Atmospheric Radiation Measurement Program in May, 1997, to the Office of Naval Research's Marine Meteorology Program, and to programs of opportunity. In addition, we believe that this work has commercial application, particularly in the area of aviation safety and planing.

LDRD FUNDING:

FY 1995	
FY 1996	\$77,893
FY 1997 (est.)	\$116,000

02/23/96 19:19
 BASE REF 19 RES
 124 NM 54 NM RES
 02/23/96 19:07
 RDA:KOKX 40/51/57N
 198 FT 72/51/50W
 ELEV= 1.5 DEG
 MODE B / 31
 CNTR 67DEG 4NM
 MAX= 24 DBZ

ND DBZ

-28
 -24
 -20
 -16
 -12
 -8
 -4
 0
 4
 8
 12
 16
 20
 24
 28

49 km

Studies of Nano-scale Structural Defects Using Advanced Electron Diffraction and Imaging Techniques

Yimei Zhu

96-22

PROJECT DESCRIPTION:

Facing the challenge of understanding the charge carriers in high-temperature superconductors, we explored and developed novel techniques to observe the distribution of charge in materials using advanced electron diffraction and imaging. In addition to demonstrating that electron diffraction at small scattering angles is very sensitive to the charge transfer in crystals, we, for the first time, successfully addressed the spatial distribution of electrons and holes on a nano-meter scale in $\text{YBa}_2\text{Cu}_3\text{O}_7$ and $\text{Bi}_2\text{Sr}_2\text{CaCu}_3\text{O}_8$ superconductors.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

***Purpose:** Understanding the electronic structure of materials is crucial to understanding the behaviors of materials. A good example is the high-temperature superconductors. Although charge distribution has been studied by x-ray diffraction, the study was limited only to simple, perfect crystals with a small unit-cell. In principle, electron diffraction is very sensitive to the ionicity of materials especially for crystals with a large unit-cell; however, a detailed investigation has never been made due to the lack of a proper method and suitable samples. Thus, exploring the possibilities and developing a new technique to study charge distribution in high Tc*

superconductors on a nano-scale using Transmission Electron Microscopy (TEM) will be of significant importance to the field of materials science and to solid-state physics; the studies are expected to reveal fundamental structural information on these technologically important materials.

***Approach:** The approach of our investigation was to use advanced TEM techniques aided by state-of-the-art computer simulation of electron diffraction and images. In studying $\text{Bi}_2\text{Sr}_2\text{CaCu}_2\text{O}_8$ superconductors, we focused on the superlattice reflections at small scattering angles which are very sensitive to charge modulation. To investigate charge distribution in $\text{YBa}_2\text{Cu}_3\text{O}_7$ superconductors, we developed a novel shadow-imaging technique that allows us to simultaneously record a systematic row of diffraction intensities as a function of crystal thickness, and thus, enables us to examine charge transfer. In both cases, the experimental observations were compared with the calculated ones using models with different charge valencies and distributions based on theoretical data on the electronic structure of these materials.*

***Technical Progress and Results:** We first investigated the sensitivity of incident electrons to charge transfer in high-temperature superconductors. Figure 1 compares the scattering amplitude of an electron hole, or a stripped hydrogen atom H^+ , with that of a neutral Bi atom. We found that the scattering amplitude of the hole is larger than that of the high-Z neutral Bi atom at small angles, e.g., 011 and 002 reflections in $\text{Bi}_2\text{Sr}_2\text{CaCu}_3\text{O}_8$, and that the electron scattering amplitude of any charged ion approaches that of H^+ multiplied by the excess charge, or valency.*

Figure 1 Electron scattering amplitude of an electron hole and a Bi atom at small scattering angles.

Figure 2 shows an experimental high-resolution image of the structural modulation viewed along the $[100]$ direction in $\text{Bi}_2\text{Sr}_2\text{CaCu}_2\text{O}_8$. The displacive superlattice structure, with a size of $2.69\text{nm} \times 3.06\text{nm}$ and a body-centered symmetry, is clearly visible. The dark cage-like contrast located in the corner and center of the cell (also see the inset), which could not be interpreted by conventional TEM, was explained in our study as the pile-up of electrons in the double BiO layer. The inset of Fig. 2 is the simulated image which matches the experimental observation very well and was calculated based on a model superimposing periodic lattice displacement (Fig. 2(a)) and charge transfer (Fig. 2(b) where an open circle denotes a hole in the CuO_2 planes, and a black dot denotes an electron in the BiO plane, with the different sizes representing different extents of occupancy).

Figure 2 High-resolution image of the structural modulation in $\text{Bi}_2\text{Sr}_2\text{CaCu}_2\text{O}_8$. The embedded image is a calculated one, using a model based on the superposition of lattice displacement (a) and charge transfer (b).

Figure 3 Electron diffraction pattern of the (001) reciprocal row together with a line scan of the intensity profile in $\text{YBa}_2\text{Cu}_3\text{O}_7$ using a technique involving parallel recording of diffraction intensities as a function of thickness.

Since $\text{YBa}_2\text{Cu}_3\text{O}_7$ does not have superlattice structure, charge distribution was studied using our newly developed shadow-imaging technique. Figure 3 is an example showing the diffraction pattern of the (001) reciprocal row in $\text{YBa}_2\text{Cu}_3\text{O}_7$ using parallel recording of diffraction intensities as a function of thickness, together with a line scan of the intensity profile. Through quantitative analysis of these intensity profiles, we determined the amplitudes and phases of Bragg reflections at low scattering angles. The determined value of the structure factors, especially for the (001) reflection which is very sensitive to the distribution of valence electron in the crystal unit-cell, suggests that in the purely ionic model $76 \pm 8\%$ of the electron holes are located in the CuO_2 planes, and the rest in the CuO chain-plane of fully oxygenated samples.

PAPERS/JOURNALS/PUBLICATIONS:

A manuscript describing the results is currently in preparation.

LDRD FUNDING:

FY 1996	\$102,697
FY 1997 (est.)	\$135,000

Research into New Database Methodology Based on the Object Protocol Model

*Enrique E. Abola and
Joel L. Sussman*

96-26

PROJECT DESCRIPTION:

Rapid development in structural and molecular biology has resulted in a dramatic increase in the size and complexity of data that must be captured in database systems. Researchers require immediate access to these data using query systems that are powerful, intuitive, and allow questions to be cast using natural language constructs. Specific objectives include construction of a database system that can access all data and knowledge inherent in PDB entries. It also includes development of tools and protocols that identify, access, and return data related to PDB objects which reside in other biological and chemical databases.

This project aims at addressing issues such as data representation and data access in structural biology using the contents of the Protein Data Bank. Results of the study will help us develop a deeper understanding of what is required to build systems that address user demands, expected to increase dramatically in the near future. The work will develop computational tools that enhance PDB's database and its query system.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: The primary objective of this study is to develop a database system capable of answering complex ad-hoc queries on biological systems. For example, researchers doing drug-design studies are interested in

characterizing interactions between proteins and ligands. Questions such as "what residues in an HIV protease are directly involved in binding known inhibitors." Another interesting question is - "What is the effect of a specific mutation to the stability of the protein?" - this question may be asked by one with sequences of a family of proteins along with mutants for which no structures have been reported. The database query system will require access to programs that do homology building, sequence threading, sequence comparison, structure comparison, molecular viewing, etc. before answers may be returned.

The system being developed must be capable of answering these diverse questions. It must be highly flexible, easily extended or modified to reflect our changing understanding of biological processes. It must be interconnected to other databases. It also must be capable of using new computational tools as they arise.

Approach: Data modeling work needed to support the activities described above are being done starting from the 3DB schema developed primarily to support data archival activities as well as some user generated ad-hoc queries. Enhancements to the schema are being generated from user feedback, interactions with close collaborators and from our own studies.

Users are being asked to submit specific queries. These are then being used to test the schema and to identify computational tools that must be integrated into the system.

The use of other modeling and database development environment will be attempted after initial studies using the Object Protocol Model (OPM) system are completed.

Technical Progress and Results: We have started to make significant changes to the current 3DB schema based on discussions with users and other collaborators. These changes include a redesign of several base classes and the introduction of a number of new classes. The schema and a data browser are available for perusal through the web (URL - <http://terminator.pdb.bnl.gov:4148>).

Our primary collaborator in this project, Dr. Victor Markowitz, from Lawrence Berkeley National Laboratory (LBNL), has delivered a new version of the OPM schema editor tool as well as the first version of the Object Query Tool (OQT). We are using the schema editor for our design work and are currently evaluating the OQT and its various interfaces for returning answers to queries.

We have started the task of identifying programs that we will integrate in the first full system that we develop. We shortly will be working with the OPM group to find ways of extending OPM to include methods that operate on objects. For example, we are currently evaluating the use of methodology for describing protein-protein and protein-ligand interactions developed by one of our

collaborators, Dr. Vladimir Sobolev, from the Weizmann Institute of Sciences as a method to be attached to the object class Residue Molecule. Sobolev's program is capable of answering the question -- "What residues are interacting with a ligand in a protein?" The answer returned not only identifies that ligand binding site residues but also characterizes the nature of the chemical interaction.

Work on the project just recently started (August, 1996) and we therefore anticipate further significant progress in the coming months.

We have modified our plans regarding the development of the prototype Object Oriented Database (OODB) described in our proposal. At this time, we will not pursue the collaboration with Dr. Major from the University of Montreal but will instead work with Dr. Otto Ritter, who will Head the PDB Informatics R&D group on the OODB work.

LDRD FUNDING:

FY 1996	\$ 14,394
FY 1997 (est.)	\$100,000
FY 1998 (est.)	\$ 95,000

Tailored Pulse UV/XUV Photon Source Development

*Louis F. DiMauro and
Erik D. Johnson*

96-27

PROJECT DESCRIPTION:

The arbitrary shaping of temporal lasers pulses at visible and ultraviolet wavelengths is being studied. Applications include the design of an optimal pulse shaped for efficient photoemission from an ejector rf-electron gun for linear accelerators. Additional investigations are also proposed on the production of high harmonic radiation above 10 eV photon energies for use as a seed pulse in the UP-FEL project at the Source Development Laboratory.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: BNL has launched several accelerator-based initiatives in recent years which rely upon the production and control of intense, short pulse, UV and VUV/XUV radiation. The 10 MeV Pulsed Radiolysis Facility (CRCR), the Accelerator Test Facility and the Source Development Laboratory (SDL) are all based on photocathode electron guns which require a short wavelength (UV) drive laser, with the latter having the additional requirement of a synchronized VUV/XUV injector beam for the UP-FEL project. Optimization of these experiments can be achieved in part by direct control over the temporal profile of the radiation pulse. One aim of this project is to develop strategies of efficient production and control of arbitrary pulse shaping in the UV-XUV range. Sources of this type will also be valuable tools for optimal control methods in atomic, optical, chemical and materials science. The second

objective is directed at the development of a high harmonic source of coherent XUV radiation as a primary and sub-harmonic injector beam for the UP-FEL project. This development can be pivotal in extending the advantages of the seeded beam approach to FELs into the soft x-ray regime. The research proposed in this document remains a necessary and vital "missing" component for numerous BNL initiatives.

Approach: Rapid advances in optical engineering, such as the advent of chirped pulse amplification (CPA) to generate intense, ultra-short visible laser pulses and progress in the optical telecommunication sciences, has provided the tools necessary for the production of arbitrarily shaped pulses of coherent radiation. The experimental challenge is to synthesize these techniques and create intense, encoded UV-XUV coherent pulses. The fundamental principle is that an ultra-short laser pulse is governed by a simple transform relationship that connects the pulse duration with its bandwidth. The shorter the pulse is in time, the larger is the bandwidth associated with the laser's central frequency. Chirped pulse amplification makes use of this simple relationship for amplifying ultra-short pulses to gigawatt or greater peak powers while minimizing the potential for optical damage to critical amplifier components. The actual implementation of the CPA technique is accomplished by the use of dispersive optical elements, i.e. gratings, prisms, before and after amplification and is illustrated in Fig. 1. A *weak*, ultra-short pulse first enters a stretcher apparatus which elongates the pulse in time by at least a factor of a thousand. This enables the efficient extraction of gain from the amplifier medium by lowering the peak power of the pulse by the same factor. Once the gain has been extracted the *amplified* pulse is ejected into the compressor which reconstructs the temporal shape of the input

pulse but with increased power (by a factor of 10^6). Thus, the stretcher and compressor provide the proper mathematical optical transform function for performing this operation.

Figure 1 Chirped pulse amplification scheme.

The physical arrangement of the stretcher allows the incorporation of additional optical components which permits the controlled alteration of the input spectrum. The spectrum is altered in such a way that its transform after the compressor gives the desired pulse shape which differs from the original input pulse. For instance, proper modulation of the frequency spectrum of a temporal gaussian input pulse in the stretcher will transform it into a temporal square wave pulse following compression. It is easy to imagine that illumination of a photo-cathode with a square pulse will produce a more uniform electron beam as compared to a standard gaussian envelope. The technical development involves the extension of known shaping techniques and principles used for low powered visible beams into the high powered, UV range.

Technical Progress and Results: We have begun examining designs and diagnostics for an arbitrary pulse shaper. Implantation of these designs into a CPA titanium sapphire laser system awaits completion of the laser laboratory room within the Source Development Laboratory (Building 729). The laser is a Spectra-Physics/Positive Light system purchased by the NSLS in FY1996. This laser is capable of delivering 60 fs, 50 mJ, 800 nm pulses at a 10 Hz repetition rate.

Synchronization to the LINAC is achieved by matching the laser oscillator's cavity length to a sub-harmonic of the LINAC's rf-source. Optical tables and hardware for the shaping apparatus have also been ordered and received. The laser laboratory space within the SDL building is provided by a 400 sq. ft., class 1000-grade clean room environment. Delivery is expected in late January 1997 and laser installation will proceed shortly thereafter.

A future requirement for the UP-FEL project is the need for a coherent VUV/XUV source of seed radiation in the 100-50 nm range. Generation of high harmonic radiation from high density inert gas jets produced by intense field irradiation is one viable seed source. The major engineering issue is the effective coupling of the high harmonic radiation into the experimental target chamber, i.e. the UP-FEL wiggler. Optimization of the harmonic throughput onto a target depends upon a number of experimental parameters, i.e. optics, phase matching. However, one key factor is the ability to efficiently separate the collinear harmonic radiation from the more intense, fundamental drive laser beam. Standard separation using dispersive techniques often results in hundred-fold losses. We have developed a novel excitation geometry for producing near gaussian spatial harmonic beams while making separation from the intense fundamental drive beam simple and efficient. Based on simple phase-matching considerations, a drive beam with a doughnut-like transverse spatial mode will produce *on-axis* harmonics in a near gaussian mode distribution due to conservation of momentum. Consequently, separation of the high harmonics from the drive laser is readily achieved by placement of a circular aperture which passes the harmonics but blocks the fundamental beam. The technique has been demonstrated by our collaborator, Dr. Pierre

Agostini (Saclay, France). The experiments were performed in Saclay laser laboratory using an argon gas jet irradiated by a 100 fs, 800 nm (1.5 eV) fundamental beam with a doughnut-like mode. Argon gas exposed to an intensity of 0.3 PW/cm^2 will produce up to the 35th harmonic (53 eV). Figure 2 shows a CCD camera image of the 17th harmonic (25 eV photon energy) produced by this experimental geometry. The harmonic beam is circular and bright, containing approximately 10^9 photons per shot.

Figure 2 Spatial profile of the 17th harmonic beam produced by strong-field excitation.

LDRD FUNDING:

FY 1996	\$71,570
FY 1997 (est.)	\$115,000

Methods for Detecting Activation of the DNA- Activated Protein Kinase, DNA-PK, in Human Tissue Culture Cells

Carl W. Anderson

96-32

PROJECT DESCRIPTION:

DNA-PK is a nuclear serine/threonine protein kinase composed of a large (>4000 amino acids) catalytic polypeptide, DNA-PK_{cat}, and Ku, a heterodimeric human autoantigen that binds DNA and targets DNA-PK_{cat} to it. *In vitro*, DNA-PK is activated by DNA ends and DNAs with single-to-double strand transitions (e.g. nicks, gaps, or breaks). DNA-PK phosphorylates several nuclear, DNA-binding proteins including the p53 tumor suppressor protein. These properties suggest that DNA-PK may function to detect DNA damage and initiate cellular responses. Recent studies have shown that DNA-PK is required for double-strand break repair and site-specific (V(D)J) recombination in mammalian cells.

Currently, it is not possible to measure DNA-PK activity in living cells; thus, it has not been possible to determine if DNA-PK is activated by DNA damage or by natural nuclear processes (e.g. DNA replication, transcription, recombination) that produce DNA structures similar to those that activated DNA-PK *in vitro*. To identify factors that activate DNA-PK in human tissue culture cells, we propose to develop methods to access the activity state of DNA-PK in living cells. We also will modify our current radioactive assay for DNA-PK to a fluorescence-based assay that will be suitable for screening potential inhibitors using a

robotic assay.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: The human genome is organized into 23 pairs of chromosomes. Each chromosome contains two very long DNA strands each of which consists of a linear chain of about 20,000,000 to 500,000,000 nucleotides. A critical problem in cell biology is maintaining the integrity of the DNA genome. Normal chemical and physiological processes cause tens of thousands of damage events per day, and external agents including X-rays and UV radiation also damage DNA. A single unrepaired double-strand DNA break may result in cell death, and unrepaired or improperly repaired DNA damage may lead to cancer. Human cells have several mechanisms for repairing DNA damage; they also have "checkpoint" mechanisms that prevent DNA replication and cell division (or that cause cell death) when DNA is damaged. One critical component in the DNA damage response mechanisms is the p53 tumor suppressor protein. p53 is a transcription factor that controls the expression of several genes that arrest cell cycle progression when DNA is damaged.

Although rapid progress has been made in characterizing DNA repair mechanisms and the cellular response to DNA damage, little is known about how damage is detected. Studies in yeasts have shown that protein kinases are important elements in the regulatory circuits that control cell cycle progression in response to DNA damage. A strong candidate for a human enzyme that detects DNA strand breaks is the DNA-activated protein kinase, DNA-PK. However, methods are needed for determining the activity state of DNA-PK in cells so that the agents and conditions that activate DNA-PK can be identified and activation can

be correlated with the biochemical mechanisms that govern the cellular response to genotoxic stress.

A major factor limiting the effectiveness of present cancer treatments is the relative resistance of cells to therapeutic treatments and the emergence of radio-resistant or drug-resistant tumor cells. Drugs that inhibit the repair of DNA strand breaks should increase the sensitivity of tumor cells to radiation and drug treatment. Thus, inhibitors of DNA-PK may be effective enhancers of genotoxic drugs for improved cancer therapy. In order to make screening for DNA-PK inhibitors practical, a robust non-radioactive assay for DNA-PK activity is required.

Approach: First, we are characterizing the phosphorylation of human p53 and will determine whether specific sites are under-phosphorylated in p53 from human tumor cells that lack DNA-PK activity. These studies will show whether p53 (and, as resources permit, other putative substrates) are phosphorylated *in vivo* at sites that are phosphorylated by DNA-PK *in vitro*. Second, we will select and characterize human cell lines that express recombinant DNA-PK substrates. We hope to produce substrates that are expressed efficiently in human cells and that are phosphorylated specifically by DNA-PK. The phosphorylation state of these substrates then should reflect the intracellular activity state of DNA-PK. Third, we will develop polyclonal or monoclonal antisera that specifically recognizes p53 phosphorylated at the serine 15 site. This antisera will allow us to determine when p53 becomes phosphorylated at the DNA-PK site and to identify physiological factors that affect phosphorylation at this site. If serine 15 of p53 is phosphorylated primarily by DNA-PK *in vivo*, the antisera will provide a second method for determining the activity state of DNA-PK. Finally, we will design

fluorescence-tagged peptide substrates that can be used in conjunction with our phosphopeptide-recognizing antisera to measure DNA-PK activity without a need for radioactive precursors.

Technical Progress and Results: Previously, we reported the sequence of a cDNA corresponding to the DNA-PK_{cs} polypeptide. Analysis of additional cDNA clones from a human T-cell library corresponding to the carboxy-terminal kinase domain revealed a 93 bp segment in four of five independent clones that was not present in the cDNA initially isolated from HeLa cells. The 93 bp segment appears to represent an exon that encodes 31 amino acids. RT-PCR showed that most DNA-PK_{cs} mRNAs in human cells have this exon. Thus, the nascent DNA-PK_{cs} polypeptide is composed of 4127 amino acid and has a predicted mol. wt. of 469,021 (470 kDa). A manuscript describing our analysis is in press.

The carboxy-terminal segment of the human p53 tumor suppressor protein, containing the tetramerization domain and the single-stranded DNA binding domain, is phosphorylated at at least two evolutionarily conserved sites, serines 312 and 392; a third site can be phosphorylated *in vitro* by protein kinase C. Another group has suggested that DNA-PK phosphorylates a site near the carboxy terminus of p53. To determine the biochemical consequences of phosphorylation at these sites, a segment condensation method that permits chemical synthesis of large (>90 amino acid) phosphopeptides was used to produce phosphorylated and non-phosphorylated derivatives of the carboxy-terminal tetramerization and regulatory domain of human p53 (residues 303 to 393). The five differentially phosphorylated, synthetic p53 peptides exhibited monomer-tetramer association as determined by analytical ultracentrifugation. Circular

dichroism spectroscopy revealed that phosphorylation at Ser315 induced an increase in α -helical content that was abolished when Ser392 also was phosphorylated, suggesting an interaction between N-terminal and C-terminal residues of the C-terminal domain of p53. Phosphorylation at serine 392 decreased the dissociation constant for tetramer formation 10-fold. Phosphorylation at serine 312 by itself had no effect on tetramer formation, but phosphorylation at this site negated the effect of phosphorylation at serine 392. The magnitude of the dissociation constant is consistent with a role for phosphorylation in controlling the formation of p53 tetramers in normal cells. Manuscripts describing these studies are in press and in preparation.

To detect phosphorylation of p53 at serine 15, the site putatively phosphorylated by DNA-PK, we are attempting to produce antibodies that specifically recognize p53 only when phosphorylated at this site. Immunization of a rabbit with a phosphorylated peptide corresponding to the Ser15 site yielded polyclonal sera that was only marginally specific for the phosphorylated peptide. Immunization of mice with the same peptide yielded 49 hybridoma cell lines that reacted equally well with the phosphorylated and dephosphorylated peptide. These results suggest that the immunizing peptide is rapidly

dephosphorylated after injection. Efforts to synthesize modified phosphopeptides that should be resistant to dephosphorylation currently are in progress.

PAPERS/JOURNALS/PUBLICATIONS:

Connelly, M. A., H. Zhang, J. Kieleczawa, and C. W. Anderson. 1996. Alternate splice-site utilization in the gene for the catalytic subunit of the DNA-activated protein kinase, DNA-PK_{cs}. *Gene* (in press).

Sakamoto, H., H. Kodama, Y. Higashimoto, M. Kondo, M. S. Lewis, C. W. Anderson, E. Appella, and K. Sakaguchi. Chemical synthesis of phosphorylated peptides of the carboxy-terminal domain of human p53 by a segment condensation method. *Int. J. Peptide Protein Res.* (in press).

FOLLOW-ON FUNDING:

NIH Grant R01 GM52825-01A1, 5/1/96-4/30/00, Function of the Human DNA-Activated Protein Kinase, P.I. Carl W. Anderson, 5/1/96-4/30/97 \$259,185; 5/1/96-4/30/00 \$1,025,744.

LDRD FUNDING:

FY 1996	\$101,639
FY 1997 (est.)	\$109,000

Enzymatic and Regulatory Interactions of a Single Protein with Three Different Sites in Nucleic Acids

Sanford A. Lacks

96-34

PROJECT DESCRIPTION:

The DpnM protein, a DNA methylase, was produced and crystallized in our laboratory, and its structure is being determined by x-ray crystallography at the NSLS in collaboration with Z. R. Korszun and A. Tran. In addition to its enzymatic function, in which it binds to GATC sites in DNA and methylates the adenine residue, preliminary evidence suggested that the protein may have two regulatory functions in which it binds to two other sites in DNA and RNA, respectively. The aim of this proposal is to test whether this enzymatic protein does have regulatory functions in which it binds to nucleic acids and, if so, to identify the sequences of the regulatory binding sites in DNA and RNA, and to crystallize the DpnM protein with appropriate oligonucleotides. The DpnM protein will also be crystallized with a GATC-containing oligonucleotide, to which it has already been shown to bind, and the structures of the three different complexes will be determined by x-ray crystallography. In the event that one or both of the regulatory functions do not implicate the DpnM protein directly, the actual mechanisms of these regulatory processes will be explored and determined.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: The aim of this work is to elucidate several unusual mechanisms regulating gene expression in *Streptococcus*

pneumoniae, which is a prominent bacterial pathogen. Cells of this species contain either the *DpnI* or *DpnII* restriction-modification systems encoded by interchangeable genetic cassettes. The *DpnI* endonuclease recognizes and cleaves methylated GmeATC, whereas the *DpnII* system methylates GATC and cuts unmethylated GATC. Therefore, the two systems should be mutually exclusive. However, plasmids carrying the *DpnI* cassette can be established in *S. pneumoniae* host cells carrying a functional *DpnII* cassette, but the *DpnI* genes are turned off. Also, under various circumstances, expression of *DpnII* genes can be turned on or off. If, as suggested by preliminary evidence, one of the proteins produced by the *DpnII* system, DpnM, which functions enzymatically to methylate the cell's own DNA and thereby prevent its cleavage by the *DpnII* endonuclease, also participates in these regulatory processes, then this single protein may bind to nucleic acids in three different ways. If such binding is found, then the interaction of the protein with the nucleic acids will be investigated by x-ray crystallography. At the very least, the enzymatic complex of DpnM and DNA will be examined.

The *DpnII* cassette contains three genes, *dpnM*, *dpnA*, and *dpnB*, which respectively encode two methylases, DpnM and DpnA, capable of methylating GATC, and the endonuclease, DpnB, in that order. Under steady-state production of the enzymes, a putative promoter (P_0) upstream from the *dpnM* gene is turned off, possibly by binding to DpnM; it may be turned on when DpnM is deficient, as when the system is introduced into a "naive" cell, to increase transcription of the *dpnM* gene. DpnM might block such transcription by directly binding to DNA at P_0 . In the steady state, *dpnM* was shown to be transcribed from a promoter (P_1) immediately adjacent to it so that the mRNA contains no ribosome-binding site upstream of *dpnM*. A third promoter (P_2) transcribes only the

downstream *dpnA* and *dpnB* genes. Another possible regulatory function for DpnM, involving the *DpnI* cassette, may be in blocking translation from mRNA containing the *dpnC* gene, which encodes the endonuclease *DpnI* that cleaves methylated (GmeATC) sites. When *dpnC* is introduced into a DpnM-containing cell, its mRNA is made, but no *DpnI* protein is produced, which suggests that its translation is blocked, possibly by binding of DpnM to the mRNA.

Only a few cases of regulatory function of an enzyme binding to DNA or RNA and affecting gene expression have been reported. In none of them has the structural basis of the interaction been determined. It will be remarkable if the DpnM protein is capable of regulating gene expression at the levels of both transcription and translation. Determining whether the protein sites of interaction with the different nucleic acid sites are distinct or overlapping would be of great interest. However, other mechanisms might be responsible for the observed regulatory phenomena, and their elucidation could also be valuable. In either case, this work should enhance our understanding of both the regulation of gene expression and the interaction of proteins with nucleic acids.

Approach: Three separate aspects to be dealt with are: (1) Analysis of promoter P_0 and the effect of DpnM on its function; (2) The effect of DpnM on expression of *DpnI* in methylating strains; and (3) Crystallography of the *DpnII* system proteins and their complexes with nucleic acids. During this past year a fourth aspect emerged, the nature and regulation of promoter P_2 in the *DpnII* system.

To study P_0 , a reporter vector capable of measuring the promoter function in the absence of the *dpnM* gene was required. This would entail the design and construction of a plasmid capable of growth in *S. pneumoniae*

and expression of an easily measured gene product, such as chloramphenicol acetyl transferase (CAT). Provision must be made for facile interchange of promoter segments. A vector allowing also interchange of ribosome-binding sites would be particularly useful for the investigation of *DpnII* system regulation. Introduction into such a vector of various DNA segments in the region of P_0 and measurement of the CAT product in strains with and without DpnM will allow assessment of P_0 promoter activity and its inhibition by DpnM. The reporter vectors will also be used to investigate the nature and expression of the P_2 promoter.

The effect of DpnM on *DpnI* expression will be explored in three ways. First, inasmuch as a substantial amount of the DpnM protein is available, the protein can be used in gel retardation assays for evidence of its binding to specifically labeled *DpnI* cassette mRNA. In such assays, binding of a protein to the nucleic acid retards the migration of the nucleic acid in gel electrophoresis. Second, the ability of *DpnI* plasmids to be established in *DpnII* host cells defective in the *dpnM* gene, but still methylating their DNA by the action of DpnA, will be tested. Third, the leader sequence between the *DpnI* cassette mRNA start site and the ribosome binding site, which is the presumptive target for DpnM binding, can be removed by appropriately deleting DNA in the *DpnI* plasmid. The altered plasmid will be tested for establishment in a *DpnII* cell to see whether this region is essential for blocking *DpnI* expression.

The crystallographic determination of the DpnM protein structure will be completed. Currently, analysis of a complex of the protein and its cofactor, S-adenosylmethionine (SAM) is nearing completion. Attempts will be made to crystallize the DpnM protein together with a GATC-containing DNA oligonucleotide. Gel retardation showed that

the protein binds such oligonucleotides, and we shall vary the crystallization conditions and test a variety of oligonucleotides of different length, since other workers have shown crystallization of protein-oligonucleotide complexes to be dependent on oligonucleotide length. Similar approaches will be taken with the regulatory complexes, if they are established. Once we obtain highly diffracting crystals of the DpnM-oligonucleotide complexes and collect data from them at the NSLS, we should readily determine their structures by molecular replacement of the DpnM moiety. Crystals of the DpnB protein (the *DpnII* endonuclease) complexed to DNA will also be analyzed to see how this protein binds to the GATC site.

Technical Progress and Results:

Construction of reporter vectors: Reporter vectors based on the streptococcal plasmid pLS1 were constructed by introducing the *cat* gene from the staphylococcal plasmid pC194, which encodes a chloramphenicol acetyltransferase (CAT). Restriction sites were strategically positioned upstream from the *cat* coding region to allow insertion of DNA segments containing putative promoters and ribosome-binding sites. Promoter activity was measured by the amount of CAT present in cultures containing the plasmid. The CAT activity was assayed photometrically in cell extracts after addition of chloramphenicol.

Test of P_0 promoter: With a demonstrated promoter, such as P_1 , and a Shine-Dalgarno ribosome-binding sequence in the reporter vector, considerable activity, equal to 360 units, was observed. When a DNA segment from the *DpnII* cassette that included the putative P_0 promoter substituted for P_1 , no activity (<1 unit) was observed. Although this finding indicated an absence of promoter activity despite the presence of a consensus promoter sequence, closer examination of the segment cloned showed that an upstream transcription terminator (for the adjacent *orfL*

gene) formed a hairpin that included the -35 box of the putative promoter. It is possible that this hairpin formed in the supercoiled reporter plasmid and prevented the promoter from functioning. Therefore, a shorter segment containing P_0 but not the hairpin will be tested. Only if we can demonstrate P_0 promoter activity can we test for its inhibition by DpnM.

Translational repression of *DpnI* expression: To see whether DpnM could bind *DpnI* mRNA, we prepared a synthetic RNA (after cloning the *dpnC* gene and associated upstream DNA in the transcription vector pGEM3Z) that corresponded to the first 273 nucleotides of the natural mRNA. This segment was expressed from the SP6 RNA polymerase promoter in the cloning vector to give an RNA molecule corresponding to the leader portion and some of the coding region for *DpnI* mRNA. The RNA, which was radioactively labeled, was subjected to gel electrophoresis in the presence of various amounts of DpnM protein. No retardation of the RNA migration was observed in the presence of DpnM. To see whether the repression required the DpnM protein *in vivo*, we constructed a host strain of *S. pneumoniae* that carried the *DpnII* cassette in its chromosome but with an insertion in the *dpnM* gene. This mutant host still methylated its DNA since it produced the DpnA methylase and the *DpnII* endonuclease, presumably from a transcript starting at the P_2 promoter. The absence of DpnM did not prevent a *DpnI* plasmid from establishment. Thus, neither approach taken to this question supports the hypothesis that the repression results from DpnM binding to the mRNA. The mechanism for this repression remains unknown.

Location and regulation of the P_2 promoter: In the above construction of a host strain with a *DpnII* cassette in the chromosome that was defective in *dpnM*, we

encountered an unusual behavior of the P_2 promoter. When cultures were grown maximally and held for several hours in stationary phase, the P_2 promoter lost its ability to function, as manifested by the cessation of DpnA methylase and DpnB endonuclease production. That the change was not in the promoter itself or in the downstream genes was shown by transferring the *DpnII* chromosomal segment to a plasmid and demonstrating methylase activity when that plasmid was in a normal host able to support P_2 function. Furthermore, plasmids containing *DpnII* cassettes identical to that originally in the chromosome did not express P_2 function when introduced into the altered host cells. We hypothesize that P_2 requires an unusual sigma factor, which is not available in the altered cells. Previous demonstration of the P_2 transcript start site showed no typical promoter consensus sequence in its vicinity. Currently, we demonstrated P_2 promoter activity in our reporter vector, and we have localized the promoter to a 36-base-pair sequence. We plan to identify the promoter recognition sequence and further investigate its regulatory mechanism.

Crystallographic analysis of *DpnII* proteins: It turned out that we were overly optimistic in thinking that the DpnM structure was solved. The putative solution was based on fitting our crystallographic data by molecular replacement to the structural fold of a DNA cytosine methylase. But it was not possible to refine that "solution", probably because DpnM, which is a DNA adenine methylase, has a different fold. However, during this past year we succeeded in growing large crystals of DpnM complexed with its SAM cofactor. Using frozen crystals that had been soaked with mercury ions, we obtained good sets of data to 2.6 Å for multiple wavelengths at the NSLS stations X12B and X12C. With phases determined by the multi-

wavelength anomalous dispersion method, we obtained an electron density map showing alpha helices and beta sheet structure typical of proteins. Currently, we are fitting the polypeptide chain to this map, and we hope to have the DpnM structure completely solved within two months.

We have not yet succeeded in crystallizing DpnM complexed with DNA, but we have been examining crystals of DpnB-DNA complexes, for which we obtained a complete set of crystallographic data. We were able to crystallize DpnB also with an iodinated DNA oligonucleotide, and we are currently trying to obtain good data from these crystals. So far, however, their diffraction has shown too much mosaic spread to be useful for phase determinations. We also examined crystals of the complex after soaking with heavy atoms but have not yet obtained suitable derivatives. We shall try to produce better quality crystals and pursue these efforts to solve the DpnB-DNA structure.

PAPERS/JOURNALS/PUBLICATIONS:

There were no publications this year, but we envisage preparing the following papers next year: (1) Purification of DpnM methylase and its crystallization with S-adenosylmethionine. (2) Crystallographic structure of the DpnM DNA adenine methyltransferase. (3) Analysis of promoters and ribosome-binding sites in *S. pneumoniae* using a reporter vector. (4) Identification, characterization, and regulation of a promoter in *S. pneumoniae* recognized by a novel sigma factor.

LDRD FUNDING:

FY 1996	\$111,076
FY 1997 (est.)	\$119,000

Low Frequency Dynamics of Novel Materials

Myron Strongin

96-37

Dmitri Basov

G. Lawrence Carr

Victor J. Emery and

Gwyn P. Williams

PROJECT DESCRIPTION:

The purpose of this project is to use synchrotron radiation from the National Synchrotron Light Source (NSLS) as a unique source of very far infrared radiation for measurements of the properties of solids. This regime is relatively unexplored and is of crucial importance for understanding the correlated phenomena that are expected to dominate the behavior of novel materials, such as a high T_c superconductors, fullerides and organic conductors.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: This project has made a significant start in bringing research in this new area to fruition, and various important pieces have already been put in place. During this time Dmitri Basov has joined the Physics Department and has been supported under the Laboratory Directed Research and Development (LDRD) Program, and in addition G. L. Carr, an expert in far infrared properties, has joined the NSLS. During this year progress in implementing the aims of the LDRD to use the synchrotron to extend infrared measurements to the 2-200 cm^{-1} spectral region have been made possible by two important developments. First, a new initiative to study complex metals titled "Charge Transport in Complex Metals" was funded by the Materials Science Division of Basic Energy Sciences and an equipment

grant was given to Professor D. Tanner and G. L. Carr, which will be used to move the laminar grating monochromator now at the University of Florida to Brookhaven. It is this instrument that will be used for measurements down to 2 cm^{-1} .

Approach: The work in this program involves close interaction between theory and experiment. In fact, this cooperation was a major asset in making the case for receiving funding for a new program in this area. The experimental work will make use of the unique capability of the NSLS VUV ring as a source of very far infrared radiation.

Technical Progress and Results: Some initial measurements were made on the U4 infrared line at the NSLS with rather limited success and these measurements basically point to the stringent conditions needed for condensed matter measurements in the very far infrared. The stability of the apparatus and the platform are crucial, as well as the stability of the cryogenic apparatus. Another interesting problem is the quality of the vacuum system. The standard infrared spectrometers do not have sufficient room for standard pumping and some new tests of cryosurfaces are underway to see if the cryostat itself can also be used to pump the vacuum space to pressures approaching the ultra high vacuum regime. In addition to this project, a cryostat has been fitted to an existing Bruker 113 spectrometer, which has been acquired for service on the infrared beamlines when they are constructed. Until that time measurements on oxide superconductors will be made using standard IR sources. The present cryostat has been especially designed for transmission measurements and will be used for some of the thin film experiments described below.

A significant part of the work on novel materials is devoted to studies of impurity effects in the oxide superconductors. Infrared

measurements of $\text{Yb}_{1-x}\text{Cu}_x\text{O}_{6.6}$, a high- T_c superconductor, with different concentrations of Ni and Zn were performed in collaboration with Professor T. Timusk. The results indicate that the pseudogap is unaffected by Ni whereas Zn induces the appearance of intragap states. These results are presently being analyzed. It is also planned to extend these measurements to studies of $\text{Yb}_{1-x}\text{Cu}_x\text{O}_8$ compounds that are doped with Ni and Zn.

Another problem that is relevant to studies of these novel materials is the general behavior of materials near the insulator to metal transition. To better understand this problem, photoemission measurements were made on ultra thin metal films as they went from the insulating to metallic state with increasing deposition of metal. These measurements were made with a new high resolution analyzer. It is expected, in this present year, that these measurements on ultra thin metallic layers will be extended to far infrared measurements which will yield the complex conductivity. These thin films serve as a model system where the effects of strong correlations can be studied and understood, before measurements are made on the more complex metals which are the subject of this proposal. The study of these ultra thin layers is one of the reasons we have emphasized the importance of ultra-high vacuum during the experiments.

The theory component of this program has and will play a crucial role in understanding these materials. During this period there has been work on the theoretical explanation of superconductivity in the high T_c superconductors and in this present period we expect that this LDRD will support some of this work on correlated systems at low temperatures.

PAPERS/JOURNALS/PUBLICATIONS:

Huang, D.-J., Reissfeld, G. and Strongin, M. A

photoemission study of the transition from the insulating to metallic state in ultra thin layers. Phys. Rev. B: Rapid Communications (submitted).

Puchkov, A.V., Basov, D.N. and Timusk, T. Pseudogap state in high- T_c superconductors: an infrared study. J. Phys.: Condens. Matter (submitted).

Basov, D.N., Timusk, T., Thomas, G.A., Rapkine, D.H., Volkov, P., Guo, Q. and Poon S.J. Lattice dynamics of icosahedral quasicrystals: an infrared study. Phys. Rev. B (submitted).

Basov, D.N., Liang, R., Dabrowski, B., Bonn, D.A., Hardy, W.N. and Timusk, T. Pseudogap and charge dynamics in CuO_2 planes in YBCO. Phys. Rev. Lett. (submitted).

Basov, D.N., Poon, S.J. and Timusk, T. Anomalous lattice polarizability in intermetallic compounds: an infrared study. Phys. Rev. Lett. (submitted).

Two PRL papers accepted: PRL 77(15) and PRL 77(19). Two more papers are in preparation.

NSLS Users' Meeting, Brookhaven National Laboratory, May 1996.

Conference on Non-Fermi Liquid Behavior, University of Santa Barbara, Santa Barbara, California, May 1996.

International Conference on Quasicrystals, Ames National Laboratory, August 1996.

LDRD FUNDING:

FY 1996	\$77,465
FY 1997 (est.)	\$81,000

BNCT for Leukemia

Through *Ex Vivo* Purging of Bone Marrow

Jeffrey A. Coderre and
John D. Glass

96-38

PROJECT DESCRIPTION:

The overall objective of this project is to experimentally determine the feasibility of using boron neutron capture therapy (BNCT) to purge bone marrow *ex vivo* prior to autologous bone marrow transplantation. The first stage is to demonstrate selective delivery of boron to leukemia cells using boron-containing metabolite analogs, particularly the asparagine analog, 3-borono-L-alanine.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: When leukemia cannot be controlled by chemotherapy, the patient is sometimes subjected to whole-body radiation which destroys the bone marrow. Subsequent to the radiation treatment, the patient must be rescued by a marrow transplant. Matching of donor marrow is difficult and uncertain; there is a need for methods to cleanse unirradiated samples of the patients own bone marrow of malignant cells outside of the body, then to reintroduce this cleansed bone marrow in an autologous transplant after whole body irradiation. Depending on the perceived quality of donor matches for an individual patient and the success of marrow cleansing techniques, the cleansed marrow might be either the first choice for transplant or it might serve as a back-up source of marrow in case a donor transplant fails.

Approach: Our approach to cleansing bone marrow of leukemia cells is to selectively deliver boron-10 to the leukemia cells using boron-containing analogs of metabolites. Irradiation of the bone marrow sample would then selectively kill the boron-loaded leukemia cells while sparing the normal bone marrow stem cells. The principle metabolite analog being considered for selective doping of leukemia cells with B-10 is 3-borono-L-alanine. By many empirical structure-activity rules, this compound should be a functional analog of asparagine. Certain types of leukemia cells have a specific requirement for exogenous asparagine, an amino acid that normal cells generally synthesize in adequate supply for their own needs.

Synthesis: A synthetic route to 3-boronoalanine, in the racemic form with natural abundance of boron isotopes, has been reported by a difficult multistep method. The present project requires B-10 enriched compound at a minimum, with the prospect of multi-gram quantities of B-10 enriched resolved stereoisomers to follow in case of encouraging preliminary results in the biological studies. Two synthetic approaches were proposed: one using slight modifications of the published route to obtain a small quantity of B-10 enriched compound, and a second, shorter approach that involved possible difficulties but also offered the possibility of a simpler synthesis.

Determination of intracellular accumulation of boron: Oil-filtration methods used for rapid isolation of cultured cells from the culture medium are routinely used in this laboratory for screening of boron delivery to specific cell lines by particular boron-containing metabolites. Two different leukemia cell lines, one apparently requiring exogenous asparagine (sensitive to asparaginase treatment) and one

apparently not requiring exogenous asparagine (asparaginase insensitive) were proposed as models for initial screening of 3-boronoalanine as a boron-delivery vehicle.

BNCT of murine leukemia: A pair of mouse leukemia models, derived from a common cell line, one asparaginase sensitive and one asparaginase insensitive are available. These mouse tumor model systems will be used to directly test the principle of bone marrow cleansing and subsequent autologous transplantation into whole-body irradiated leukemic mice, should the preliminary biological screening assays suggest that this experiment is warranted.

Technical Progress and Results:

Synthetic Studies:

Three synthetic approaches to 3-boronoalanine have been carried out, the original published procedure and two shorter experimental approaches (one described in the original submission and another strategy that occurred to us after submission of the original proposal).

The first of the experimental approaches failed because of an unstable synthetic intermediate: boron was lost from the molecule during a reaction sequence for one of the intermediates. The second experimental approach was partly successful. Formation of cyclo-didehydroalanine from cycloserine, a published procedure, has been confirmed, but the solubility properties of the material are such that we have not found any suitable solvent for trying the direct hydroboration of the compound to form the diketopiperazine of 3-boronoalanine. This pathway may be worthy of further investigation if the biological studies create a demand for large quantities of 3-boronoalanine.

A small amount of B-10 enriched 3-boronoalanine has apparently been obtained through the published method. Forty milligrams of material showing a single ninhydrin-reactive chromatographic spot, distinct from either glycine or alanine (the most likely ninhydrin by-products) and containing approximately the expected content of B-10 has been isolated. Final confirmation of identity by spectral and analytical methods is underway. Additional quantities of synthetic intermediates are also being brought along so that we will have material for resolution of the stereoisomers should initial biological studies on the racemic material prove encouraging.

Biological Studies:

The asparaginase-sensitive and asparaginase-insensitive leukemia cell lines have been added to our collection of cell lines used in screening of boron-containing metabolite analogs. The techniques for colony formation assays (cloning in soft agar) that will be required when the biological testing reaches the cell irradiation stage have been established.

The boron compounds currently in clinical use, boronophenylalanine (BPA) and the mercaptoborane (BSH), were tested for the ability to preferentially accumulate inside the murine leukemia cell lines. Figure 1 shows the amount of intracellular boron as a function of the amount of boron in the incubation medium in the L1210 murine leukemia cell line. Boric acid is included as a non-specific reference compound with equal distribution inside and outside the cells. The slope of the line for the test compound divided by the slope of the boric acid line is termed the accumulation ratio. In Figure 1 the accumulation ratio for BSH was 1.3 and for BPA was 0.6, indicating no preferential accumulation of BPA or BSH inside these leukemia cells. Figure 2 shows

the initial results with 3-boronoalanine. Both murine leukemia cell lines (L1210, asparaginase insensitive and L5178Y, asparaginase sensitive) were incubated with 3-boronoalanine or boric acid. Relative to the boric acid reference, the intracellular accumulation observed with 3-boronoalanine was 1.9:1 in the L1210 cells and 2.5:1 in the L5178Y cells. These are very promising results. This experiment consumed about 10 mg of the 40 mg of 3-boronoalanine produced to date. Experiments are planned to repeat these results and to then further characterize the tightness and selectivity of the binding of 3-boronoalanine to the leukemia cells relative to the normal bone marrow cells.

Figure 1. Intracellular accumulation of BPA (●), BSH (▲) or boric acid (■) in L1210 murine leukemia cells.

Figure 2. Demonstration of preferential intracellular accumulation of 3-boronoalanine in L5178Y (■) or L1210 (●) murine leukemia cells relative to boric acid in L5178Y (▼) or L1210 (▲) cells.

PAPERS/JOURNALS/PUBLICATIONS:

This project is a two year feasibility study with publications and submissions of proposals for outside support to follow demonstration of feasibility.

LDRD FUNDING:

FY 1996	\$ 82,116
FY 1997	\$ 86,000

Note: This project involves animal vertebrates or human subjects.

Designer Polymers for Permeable Ground Water Barrier Applications

Dan Melamed

96-42

John Heiser and

Paul Moskowitz

PROJECT DESCRIPTION:

Organic polymers are to be developed and tested for the selective sorption of organic pollutants from contaminated ground water such as: trichloroethylene (TCE), chloroform, and 1,1,1 trichloroethane (TCA). One of the more attractive aspects of this approach is that the polymers can be easily altered to change their ability to bind pollutants. Two polymers are being tested as designer sorbents:

1) polyethyleneimine (PEI), derivatized with hydrophobic groups and 2) polymers attached to molecules that bind pollutants, in this study, cryptophanes (Figure 1). Cryptophanes have a preorganized hydrophobic cavity, previously shown to bind pollutants, such as chloroform, and TCA.

Figure 1 General Cryptophane structure

A key aspect of this project is that the

chemistry of the materials can be readily altered to enhance their ability to bind pollutants; the substituent and the cavity size of the cryptophane can be readily altered to adjust which organic molecule(s) it will bind.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: To evaluate the designer polymers for use in a permeable barrier, an accurate method for assaying the adsorption of organic compounds from water onto a specific sorbent had to be developed. This also included developing the capability to assay the concentration of organic compounds in aqueous solutions.

Since permeable barriers for environmental remediation require large amounts of sorbent, the cost of the designer polymers must be kept low. Thus this work included a synthesis of cryptophanes specifically designed to bind key halogenated hydrocarbons, which pose the greatest environmental hazards. Cryptophanes can be inexpensively synthesized.

Approach: The method of choice for assaying organic compounds in water is gas chromatography/mass spectroscopy (GC/MS). The simplest sampling method is direct aqueous injection (DAI), which allows for direct assays of the sample with minimal possibilities for sample corruption.

For modified PEI, the main industrial supplier of that polymer and its derivatives was contacted, the BASF corporation. They supplied samples of PEI derivatized with stearic acid groups, a form similar to PEI derivatives previously shown to bind organic molecules in aqueous solution.

Technical Progress and Results: The experimental protocols for preparing adsorption isotherms and DAI-GC/MS

analysis of aqueous samples turned out to be accurate and reproducible for aqueous samples in the parts per million (ppm) concentration range for both TCE and TCA.

These isotherms also showed that the modified PEI did not bind TCE. This is surprising since other PEI derivatives have been shown to bind organic molecules in aqueous solution. This may be due to subtle aspects with this derivative of PEI. For example, the BASF compounds were derivatized with amide linkages, while most of the previously studied PEI derivatives used alkylamine linkages. Also, the BASF compounds were derivatized with twice as many long chain alkyl groups than the previously studied compounds. Both structural differences could radically alter the conformation and the hydrophobic character of the modified PEI.

A cryptophane with a cavity large enough to bind many organic halocarbons found in many toxic waste streams was synthesized. To demonstrate whether the cryptophane can bind pollutants, an X-ray crystal structure determination was done. The crystal structure, (Figure 2), shows the cryptophane has no solvent molecules in its cavity, suggesting that the cryptophane failed to bind a halogenated hydrocarbon (chloroform) in solution. This result can be explained by noting that the cryptophane contains three flexible alkyl groups, allowing it to maintain a collapsed conformation as its lowest energy state, as shown in Figure 2. This collapsed conformation is much less likely to bind organic molecules. However, the syntheses of cryptophanes with a more rigid architecture are planned.

These conformationally rigid cryptophanes should bind pollutants more effectively. The redesigned cryptophanes can then be incorporated into a polymer that will make a superior sorbent material for a

permeable barrier.

The study of cryptophanes and similar

Figure 2 X-ray crystal structure of the Cryptophane used in this study. Arrows show the position of the three alkyl groups. The collapsed conformation of the cryptophane prohibits the binding of a chloroform molecule (see text).

preorganized host molecules are also being pursued for sensor materials. The specificity with which these molecules bind their target species makes them ideal as the basis for sensor elements.

PAPERS/JOURNALS/PUBLICATIONS:

A manuscript describing the structural chemistry of large cryptophanes is currently in preparation.

LDRD FUNDING:

FY 1996

\$99,088

BNCT Treatment Planning Software Proposed Modifications

Elizabeth C. Selcow

96-46

PROJECT DESCRIPTION:

The original objective of this project was to enhance the treatment planning system for the Boron Neutron Capture Therapy (BNCT) program at BNL. The specific areas of focus include integration of multi-modality image information with the treatment planning software and investigations of methods to accelerate the Monte Carlo radiation transport analysis in the software. It was later determined that in order to effect a more immediate benefit to the BNCT project, the shorter-term emphasis should concentrate on integration of image and dosimetry information for usage by clinicians evaluating the treatment planning procedures. The proposed work on the radiation transport analysis improvements was broadened to include the development of improved capabilities in the radiation transport analysis of both diagnostic imaging and treatment systems. This enhances the capabilities at the Laboratory for several of the ongoing programs in medical research, including Boron Neutron Capture Therapy, nuclear medicine imaging, and photon radiation therapy. By consequence, the project name for the second year of this research has been modified to "Medical Physics Program Development." The enhanced analytic capability in medical physics resulting from this project will better enable the Laboratory to procure long-term outside funding.

**TECHNICAL PROGRESS AND
RESULTS - Fiscal Year 1996:**

Purpose: BNCT treatment planning: This work is a collaboration with Jacek Capala, BNL Medical Department scientist, Aidan Z. Diaz, BNL resident radiation oncologist, employee of the State University of New York at Stony Brook, and Ballard Andrews, BNL Computing and Communications Division.

Boron Neutron Capture Therapy is an experimental binary radiotherapy modality for certain types of currently intractable malignancies such as Glioblastoma Multiforme (GBM) and metastatic Malignant Melanoma. The treatment planning process involves incorporating the scans from an imaging modality, such as Magnetic Resonance Imaging (MRI) or Computed Tomography (CT), with fiducial markers; a three-dimensional reconstruction of the defined anatomical regions of interest; three-dimensional Monte Carlo radiation transport analyses of the neutron irradiation from the epithermal irradiation port of the Brookhaven Medical Research Reactor; calculation of the absorbed dose distribution; identification of optimal treatment position and time of irradiation required to deliver the prescribed dose; and evaluation of the dose distribution after patient irradiation.

The development of treatment planning procedures for radiation therapy requires a detailed definition of the tumorous regions as well as a reliable and efficient method for predicting the dose delivered to the cancerous and normal tissues. The three dimensional correlation of this information will improve the clinical insight into the differential dose distributions in the anatomical regions of interest.

Radiation transport analysis of radiobiological systems: This work is a collaboration with Michael Todosow and Hans Ludewig, BNL Department of Advanced Technology.

The specific focus is to develop improved capabilities in the radiation transport analysis of diagnostic and treatment systems. This includes extracting the relevant anatomical information from a diagnostic modality, such as MRI or CT, and creating an appropriate model for a subsequent radiation transport analysis, either with Monte Carlo or deterministic methods. In order to effect maximum integration with the Laboratory's research on neuroscience, we plan to emphasize modeling of regions of the head and neck. These regions are characterized by nonregular heterogeneous volumes with multiple re-entrant surface features and are therefore difficult to represent analytically. The improvement in the radiation transport analysis includes not only the enhanced modeling capability but also the ability to reduce the calculational time requirements. This work is integrated with related Laboratory programs in the medical area.

Approach: BNCT treatment planning: The treatment planning process may be improved by integrating information from several different imaging modalities, such as MRI, Positron Emission Tomography (PET), and Single Photon Emission Computed Tomography (SPECT), together with the three-dimensional dosimetry distribution as predicted with the Monte Carlo analysis in the treatment planning software. The software, developed by Idaho National Engineering Laboratory, includes the Monte Carlo program `rtt_MC`. This code has been tailored to provide the differential absorbed dose distributions for simulations of neutron irradiation in patient treatment planning for Neutron Capture Therapy. The three-dimensional image/dosimetry integration may also be used to aide in the understanding of tumor recurrence and to develop improved treatment planning protocols.

Specifically, we have combined the output

of the radiation transport analysis code with the reconstructed MRI volume images. This facilitates evaluation of different possible treatment plans and provides better insight into the dose distribution in regions of interest. The two-dimensional radiation dose distributions are superimposed on the MRI scans after slicing the volumes along the axial, sagittal or coronal planes. Segmentation of the three-dimensional MRI data provides a rendered three-dimensional isosurface, onto which the three-dimensional dose isocontours can be mapped. This was accomplished using the commercially available IBM Visualization Data Explorer software, which provides an extensible modular programming environment for building visualization networks. This visualization has been rendered into a stereoscopic display system at the BNL Computing and Communications Division.

Radiation transport analysis of radiobiological systems: Monte Carlo radiation transport simulations of medical imaging systems are being widely used to better understand the characteristics of the acquired images, and to study the physical processes that degrade the image, such as scatter, attenuation, and noise. In SPECT systems, the patient is injected with a radiopharmaceutical that is labeled with a photon emitting radioisotope. The radiopharmaceutical has a preferential chemical uptake in specific organs or regions of the body. A collimated gamma camera revolves around the patient providing a series of planar images which are then reconstructed to produce a three-dimensional image of the radiotracer distribution in the patient. Typical radioisotopes that are used in SPECT systems for brain imaging include ^{99m}Tc , having a 140 keV photopeak and providing information on cerebral blood volume, and ^{133}Xe , having a 81 keV photopeak and providing information on cerebral blood flow. In the Monte Carlo simulations of SPECT systems, the entire imaging system is modeled and the path of

gamma rays through the patient, the collimator, and to the detector is calculated by taking into account the probabilities of various interactions along the path.

A large component of this research project, for both Fiscal Years '96 and '97, includes the radiation transport analysis of SPECT imaging systems. We are collaborating with the MIT Whitaker College of Biomedical Imaging and Computation Laboratory in order to become familiar with the science and technology of image analysis. This includes the relevant clinical concerns, the design and detection issues associated with imaging, the mathematical algorithms implemented for detection, image reconstruction, and processing, the factors contributing to image artifacts, and the specific radiation transport issues of particular concern to the simulation of imaging systems. We are also collaborating with the BNL Medical Department and integrating our analysis with the Laboratory Directed Research and Development project (#94-37): "Feasibility of SPECT in Imaging of ^{18}F FDG Accumulation in Tumors," with Gene-Jack Wang as BNL principal investigator and Peter Kuan from the State University of New York at Stony Brook.

We are simulating the projection data from several ^{18}F FDG (Fluorodeoxyglucose) SPECT experimental/clinical acquisitions obtained with the new SPECT system in the BNL Medical Department. The BNL experimental work on FDG SPECT is also being conducted in collaboration with personnel from the Department of Radiology at Stony Brook. Specifically, we are performing the Monte Carlo simulations of these systems using the SimSPECT code, an MIT modification of the Los Alamos National Laboratory MCNP code for the specific application of SPECT systems. In the analyses, we explicitly model the source,

either a phantom or patient with the specific radiotracer distribution, the surrounding transport medium, the collimator and detector. The model of the detailed distributions of the radiotracer simulates variations in the chemical uptake of the radiopharmaceutical in the patient. The photon data reaching detector, which is generated for all of the tomographic angles corresponding to the actual experiment, is then convoluted with an inverse probability distribution function that models the energy and spatial resolution of the NaI scintillation crystal. This synthetic projection data is reconstructed with the same algorithms as the acquired projection data. Typical reconstruction methods are filtered back projection and maximum likelihood estimation.

The Monte Carlo simulations can help improve the quality of the acquired images by identifying the specific physical processes which degrade the image, such as scatter and attenuation. By isolating the regions contributing to the scattered components of the images, and subsequently removing the scattered contributions, the resultant image is improved. The simulations can provide information to improve the existing scatter correction algorithms used in image processing and in particular to tailor the corrections to this specific system. The overall benefit of the analysis to the experimental project is to help in the final image evaluations, both for phantoms and patients.

Technical Progress and Results: BNCT treatment planning: We have developed a prototype for simultaneous visualization of the 2D isodose contours superimposed on MRI image scans for transfer cuts representing sagittal, coronal, and transaxial views of the brain. This prototype includes the display of the 3D isodose surfaces superimposed on the 3D reconstructed MRI

image. The following results were presented in July at the 38th Annual Meeting of the American Association of Physicists in Medicine.

Figure 1. 3D isosurface rendering of a MRI volume, exposing the tumor of a typical GBM patient prior to treatment with BNCT. Also shown are the co-registered ^{10}B isodose surfaces, computed with the treatment planning software.

Figures 2-4. 2D isodose contours produced by slicing planes through the volumes shown in Figure 1.

Figure 2. Sagittal Section.

Figure 3. Transaxial Section.

Figure 4. Coronal Section.

The isodose contours are in units of percent of peak dose and are specified in 10% intervals. For the normal brain, 100% is equivalent to approximately 12 Gray-equivalent (Gy-eq), and for the tumorous region, 100% is equivalent to approximately 60 Gy-eq.

In the next phase of this research project, we plan to further develop this capability and adapt the software interfaces to the specific clinical requirements for routine treatment planning procedures. This will facilitate more

rapid responses to particular clinical concerns. One such requirement includes the ability to compute the total volume of the residual tumor region as seen on the MRI scans prior to BNCT irradiation. The clinical interest is to correlate the total residual tumor volume with the effective prognosis of the patient undergoing BNCT. We may also include scans from other imaging modalities in the study.

Radiation transport analysis of radiobiological systems: The specific Monte Carlo analyses performed to date include SPECT simulations with point and phantom sources, using ^{99m}Tc and ^{18}F as the radiotracers. The phantom configurations consist of 5-6 spheres of varying radii filled with either radioisotope and contained in a water-filled cylinder. At the center of the phantom containing ^{18}F , a line source is positioned. The collimators modeled represent the design specifications for those used in the Picker gamma cameras in the BNL experiments. The ^{99m}Tc acquisitions (140 keV photopeak) utilize a standard parallel hole low energy high resolution (LEHR) collimator with a hexagonal hole configuration, while the ^{18}F acquisitions (511 keV photopeak) utilize a parallel hole high energy high resolution (HEHR) collimator, also with a hexagonal hole configuration. Figures 5 and 6 represent cross sectional views of the Monte Carlo models for each of these collimators, magnified to represent a 1 cm by 1 cm view of the total 40 cm by 24 cm field of view of the detector. Each hexagon represents a lead "collar" (the septum) surrounding the central hole. The comparison highlights the design differences distinguishing the two systems: the HEHR collimator has a thicker septum, larger hole diameter, and longer hole length than the LEHR design.

Figure 5. LEHR collimator model.

Figure 6. HEHR collimator model.

The simulations of the experiments for the ^{99m}Tc and ^{18}F point sources include representations of the source in air for variations in source to detector distance, and in varying thicknesses of water for a fixed distance. The results of the air calculations show the expected degradation with distance from the source in the FWHM (full-width-at-half-maximum) of the image profile at the photopeak. Comparisons of ^{18}F simulations and acquisitions have demonstrated the importance of including the specific materials

of the detector housing structure as Compton back-scatter sources, resulting in a significant scattered component in the image. This effect is much more prominent for the 511 keV source than the conventional ^{99m}Tc source. Specific comparisons of the synthetic and acquired images and profiles will be documented in a manuscript for publication in a peer reviewed journal article. In the next phase of this project, simulations will be performed of additional ^{18}F SPECT phantom acquisitions. Finally, we will use the Monte Carlo simulations to aid in the evaluation of images for patients.

Another activity we are pursuing includes the comparative analyses of Monte Carlo versus deterministic methods for the radiation transport of radiobiological systems. The objective of this work is to investigate methodologies for accelerating the computational time requirements for the Monte Carlo radiation transport analysis. This can be accomplished by either using the deterministic codes in lieu of Monte Carlo or using the deterministic methodology to reduce the statistical variance in the Monte Carlo problem. The disadvantages of a pure deterministic approach include limitations in the degree of complexity for the representation of the geometric configuration and the nuclear cross sections. A coupled Monte Carlo/deterministic approach may be the optimum methodology for many radiobiological systems characterized by highly heterogeneous regions. Specifically, we have modeled a planar SPECT acquisition with both Monte Carlo and deterministic methods, using the MCNP Monte Carlo and the TORT three-dimensional discrete ordinates codes. There are no documented comparisons of this specific nature performed to date for nuclear medicine systems. We have modeled a configuration of an actual pinhole collimator with both MCNP and TORT and performed analyses using the same

set of nuclear cross section libraries. We plan to continue with this comparative study for SPECT systems and to perform similar studies for neutron capture therapy and photon therapy systems.

In the Fiscal Year '97 continuation of this project, we also plan to perform Monte Carlo calculations for photon radiation therapy systems. The majority of treatment planning programs used for photon therapy use simple algorithms, such as pencil beam techniques, which consider scatter and attenuation correction factors in homogeneous media. There are specific clinical applications where a more detailed heterogeneous anatomical representation is required. One such example for the head and neck region is the maxillary sinuses. We will work with Aidan Diaz to perform Monte Carlo simulations of clinical dosimetry data obtained with the Photon Radiation Therapy Facility in the BNL Medical Department.

PAPERS/JOURNALS/PUBLICATIONS:

We produced a peer reviewed publication in a conference proceedings: "An Evaluation of the Monte Carlo Simulation of SPECT Projection Data Using MCNP and SimSPECT," E.C. Selcow, BNL, A. B. Dobrzeniecki, J. C. Yanch, A. Lu, M-J Belanger, Whitaker College of Health Sciences and Technology, Massachusetts Institute of Technology. This was presented at the 4th International Conference on Nuclear Engineering, New Orleans, LA, March 10-14, 1996.

We presented a paper in July 1996 at the 38th Annual Meeting of the American Association of Physicists in Medicine, entitled, "3D Representation of the Radiation Dose Produced During the Boron Neutron Capture Therapy (BNCT) of Glioblastoma Multiforme (GBM)," A.B. Andrews, J.

Capala, E.C. Selcow (BNL), F.J. Wheeler (Idaho National Engineering Laboratory).

We also have a publication in the American Nuclear Society Transactions, November 1996 and a paper presentation at the November 1996 meeting of the American Nuclear Society, "Monte Carlo Methods for the Simulation of Positron Emitters in SPECT Systems." A. B. Dobrzeniecki (MIT), E.C. Selcow (BNL), J. C. Yanch, A. Lu, M-J. Belanger (MIT), P.D.Esser (Columbia University).

A couple of manuscripts describing the initial results of these projects are in preparation for peer reviewed journal publications.

FOLLOW-ON FUNDING:

A proposal was submitted in February 1996 to the DOE Office of Health and Environmental Research to further support this work on BNCT image and dosimetry correlation. The proposal, entitled "Improvement of Radiation Therapy Treatment Planning Through Better Definition of Tumor Volumes and Dose Distributions," was developed with Jacek Capala and Aidnag Diaz. Although the proposal entered a second phase of competition, it was not selected to be funded. We will continue to solicit outside funding for this proposal.

LDRD FUNDING:

FY 1996	\$157,773
FY 1997 (est.)	\$195,000

Comparison of Mutations in Fish Melanomas so as to Determine the Wavelengths Responsible for Human Melanoma

Richard B. Setlow

96-48

PROJECT DESCRIPTION:

Our original work on the wavelengths effective in melanoma induction, using backcross hybrid fish, employed species of *Xiphophorus maculatus* and *X. couchianus*. This cross has not been well analyzed genetically but we used it because we could produce, relatively easily, the large numbers of fish needed to determine an action spectrum. More recently Rodney Nairn of the University of Texas, M.D. Anderson Science Park-Research Division, has described a new cross using *X. maculatus* (the platyfish) and *X. helleri* (the swordtail). The F₁ generation arises from a cross between *X. maculatus* female and *X. helleri* male. There are large numbers of F₁ males which when crossed with *helleri* females, give sufficient numbers of F₂ progeny for action spectrum analysis. A human melanoma gene, p16 DNA, will be used to make radioactive oligonucleotides by polymerase chain reactions that can be used to probe for the fish melanoma suppressor gene. The isolation of the fish p16 gene will permit us to determine its sequence in non tumor and in tumor tissue and so observe the mutations that arise in tumors induced by different spectral regions--313 nm (UVB), 365 nm (UVA), and 436 nm (Blue). The distribution and types of mutations (i.e. CC-TT, C-T, T-G, etc.) along the gene are characteristic signatures of the different wavelengths used to induce mutations and will give clues to the photoproducts or photosensitized reactions that give rise to the mutations--cyclobutane pyrimidine dimers at 313 and presumably

oxidation products of DNA arising from the longer wavelengths. In non pigmented cells it has been shown that the different spectral regions give rise to different mutational spectra. The fish mutations will be guides to relate the mutations observed in human melanomas to the spectral region responsible for the mutations observed in human malignant melanomas.

Sufficient numbers of tumors, at each wavelength, must be obtained to produce statistically significant mutational spectra. For cells in culture, these numbers are usually in the neighborhood of 50-100. We propose to breed the appropriate numbers of fish, irradiate them, collect the appropriate numbers of tumors, and analyze these tumors as indicated above.

The importance of this research is to determine indirectly the action spectrum obtained for human melanoma. If the action spectrum is similar to the fish spectrum, it will indicate clearly that the longer wavelengths of UV, and even visible, are effective in melanoma induction. Such a result would have clear implications for the reduction of melanoma incidence, i.e. use protection that cuts out all wavelengths, not just the sunburning ones.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: The purpose of these experiments were 1) to breed specific numbers of the backcross hybrids of *X. maculatus* crossed with *X. helleri*; 2) to irradiate sufficient numbers with specific monochromatic wavelengths so as to attempt to produce melanomas; and 3) to obtain tissue from the melanomas that would be sent to Rodney Nairn of the University of Texas for molecular analyses to identify the genes that are changed in melanomas and how the changes might depend upon wavelength.

Approach: The overall strategy was to follow the steps outlined under *Purpose*.

Technical Progress and Results: We raised and bred the appropriate fish and obtained 608 of which 209 had the, presumed, appropriate genotype as indicated by their extensive black pigment. We assumed from previous data that these fish had melanoma genes and only one tumor suppressor gene. During the period of this proposal the fish, in groups of approximately 5-20, of all genotypes were irradiated at 4 different wavelengths. At 4 months of age they were scored visually for tumors. There were no tumors in the white fish. No tumors in the speckled fish, and, at this date, 28 tumors in the black fish. Portions of tumors from 23 fish have been sent to the University of Texas for genetic analysis and possible genome sequencing. The following table is a summary of the present data.

PAPERS/JOURNALS/PUBLICATIONS:

Nairn, R.S., Morizot, D.C., Kazianis, S., Woodhead, A.D., and Setlow, R.B. Nonmammalian Models for Sunlight Carcinogenesis: Genetic Analysis of Melanoma Formation in *Xiphophorus* Hybrid Fish. Symposium-in-Print. Photochem. Photobiol. 64(3): 440-448 (1996).

International Congress on Photobiology, September 1-6, 1996, Vienna, Austria, "Action Spectrum for Melanoma Induction in Hybrid Fish of the Genus *Xiphophorus*."

LDRD FUNDING:

FY 1996 \$103,050

Note: This project involves animal vertebrates or human subjects.

Summary Report of 163B-helleri hybrid BC to date: 11/5/96					
Wavelength	Total # Fish Treated	Exposure (J/m ²)	# Black	# Black with Tumors	Tumors to R.Nairn U.Texas
control	48	0	13	2	2
313	133	1004	49	10	8
365	163	1007	48	4	3
405	130	3020	47	12	10
436	134	3002	52	not determined	
Totals:	608		209		23

Autecology of the Peconic Bay Brown Tide Organism, *Aureococcus anophagefferens*

Julie La Roche

96-49

PROJECT DESCRIPTION:

In the mid to late 1980's brown tides, algal blooms of a small species (*Aureococcus anophagefferens*), decimated the Peconic Estuary's scallop population and affected other living resources on Long Island's East End. The blooms persisted in Peconic Bay for extended periods in 1985, 1986, 1987, 1989, then disappeared for a few years. The reoccurrence of the brown tide in 1995 sparked a renewed scientific interest. Brown tides are a recurring problem in Peconic Bay and it is important that brown tide research continue until the cause of the blooms is determined. The research effort supported here aims to determine which factors control the growth of the brown tide organism in the field. A combination of laboratory and field studies have been carried out to determine the role of macro- micro- and organic nutrients on the growth and photosynthesis of *A. anophagefferens*. A retrospective analysis of a 10 year time series of physical, chemical parameters collected in the Peconic estuary was carried out.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996:

Purpose: The purpose of the LDRD is to try to understand the physical and chemical factors that give *A. anophagefferens* a competitive advantage over other algal species present in the Peconic Estuary. The long-term objectives are to gain a good understanding of the ecology of the brown

tide organism and of the natural and anthropogenic factors controlling it. This information will be passed on to the scientific community and the Suffolk County Department of Health Services in the form of peer-reviewed publications. This information may later be used by Suffolk County officials in efforts to manage the brown tides.

Approach: We are using multiple approaches to investigate the brown tide. Laboratory studies are in progress to determine optimal growth conditions of several new clonal isolates of the brown tide. These are difficult to grow in the laboratory, so the first year has concentrated on optimizing growth in cultures but laboratory experiments will be continued to look at nitrogen, phosphorus and Fe utilization by the brown tide organism. A field study was undertaken starting March 1996 in collaboration with Suffolk County officials and consists primarily of nutrient bioassays to assess which nutrients limit primary productivity in Flanders Bay throughout an annual cycle. Each week, water samples collected in Flanders Bay are enriched with nutrients, sixteen different treatments and the increase in biomass of the natural phytoplankton followed over a period of 4 to 5 days. These field experiments will also be used to assess which nutrients promote the growth of *A. anophagefferens*.

We have analyzed a 10 year historical data set supplied by Dr. R. Nuzzi of the Suffolk County Department of Health Service. This data set was first subjected to data quality control. Additional data was obtained from the U.S. Geological Survey for the North and South Fork wells located within the Peconic Estuary watershed. Data from BNL's meteorological services was also used in the retrospective analysis.

Technical Progress and Results: Our analysis of historical data led to the formulation of a new hypothesis. This hypothesis suggests that the Peconic Estuary system obtains inorganic nitrogen necessary for phytoplankton growth almost entirely from groundwater input which contains extremely high nitrate concentration (>300 uM) as a result of prior and current agricultural practices and urbanization of the North and South Forks of Long Island. We believe that brown tide blooms occur during years of low groundwater inflow because of their ability to take up organic sources of nitrogen, thus giving them a competitive advantage over other phytoplankton species which predominately utilize inorganic nitrogen species.

BNL scientists have therefore made progress towards understanding the factors controlling the brown tide occurrence and explained the apparent brown tide requirements for high salinity. Many others have previously misinterpreted the relationship between rain, salinity and brown tide in the Peconic Bay for two reasons: 1) the salinity of the Peconic Bay is controlled by groundwater seepage which is a lagged integrator of the local rainfall and 2) the salinity/growth relationship for the brown tide algae were incorrectly determined in prior investigations. Our new data, collected using both old and new isolates of the brown tide algae, indicate that the algae grow well at salinities as low as 21 PSU, prior research suggested that the algae required salinities higher than 26 PSU to grow and this salinity requirement was used to explain the link between high salinities and brown tide blooms. We have demonstrated with laboratory experiments that salinity itself does not play a central role in controlling brown tide, but rather is a marker for the amount of ground water (and thereby inorganic nitrogen) reaching the Peconic Estuary.

We have begun working on the third objective by conducting weekly bioassay experiments in Flanders Bay. The nutrient addition bioassays conducted weekly with Flanders Bay water have demonstrated that iron, silicate and phosphate additions have no effect on phytoplankton growth. In contrast, nitrogen, provided either as ammonium, nitrate or urea, invariably results in an increase in phytoplankton biomass, confirming that the Peconic Estuary is nitrogen-limited, as are most other coastal marine systems. We are currently analyzing preserved phytoplankton samples from these experiments to determine if any of the nitrogen sources preferentially enhanced the growth of *Aureococcus*.

PAPERS/JOURNALS/PUBLICATIONS:

A manuscript describing the groundwater hypothesis has been submitted to Global Change Biology. Two other manuscripts are in preparation. One manuscript describes the salinity/growth relationship for *A. anophagefferens* and will be submitted to the Journal of Phycology. The second manuscript will present the nutrient enrichment bioassays and will be submitted to the Journal of Plankton Research.

FOLLOW-ON FUNDING:

A three year grant from NOAA for FY97-99 has been awarded to the PI as part of the Brown Tide Research Initiative (BTRI). The purpose of this project is to design probes to detect iron limitation in *A. anophagefferens* (Approximately \$ 100,000 for 3 years, \$ 38,000 in FY96).

LDRD FUNDING:

FY 96	\$ 98,405
FY 97	\$ 104,000

The Development and Demonstration of Accelerator Based BNCT Capability

D. Raparia

96-50

PROJECT DESCRIPTION:

The project is to study the yield and energy spectrum of neutrons produced with a proton beam (<2.5 MeV) from a Radio Frequency Quadrupole (RFQ) Linac as an alternative source for Boron Neutron Capture Therapy, (BNCT). The major emphasis is to study the feasibility of various production target designs to optimize the yield and energy spectrum.

TECHNICAL PROGRESS AND RESULTS - Fiscal Year 1996

Purpose: The purpose of this LDRD is to study the feasibility of producing neutrons for Boron Neutron Capture Therapy, BNCT, with an accelerator rather than with a reactor. If a small proton accelerator to produce neutrons is found to be acceptable, then BNCT could become a readily available clinical procedure.

Approach: The neutron generator to provide neutron for BNCT, is based on a low energy (~ 2.5 MeV) proton beam impacting a Lithium-7 target to produce neutron by the (p,n) reactions. The necessary conditioning of the energy spectrum can be accomplished using a relatively thin zone of material between the target and the patient. Calculations indicate that the resulting neutron yield per mA of proton current is good, and the accelerator relatively straightforward.

The RFQ and Drift Tube Linac, DTL, are provided by the Chemistry Department from

Accsys Technology Inc. The Department of Advanced Technology is responsible for the target design and construction aspects. The Medical Department is responsible for the installation of the detector instrumentation. The AGS Department is responsible for management of the effort and for the installation and commissioning of the ion source, RFQ, DTL and beam transport line. Both the Physics Department and the Department of Applied Science, in conjunction with other departments, will be involved in the experimental program.

Technical Progress and Results:

(1) An extensive set of 3D Monte Carlo neutronics analysis has been carried out for a range of NIFTI and DISCOS design parameters. In summery, it is found that of the total number of neutrons generated in the lithium target, ~ 5 to 10% are available at the BNCT treatment port.

(2) The old 3 MeV Tandem Van De Graaff has been removed from the Chemistry building. The room has been cleaned, repainted, rewired and is ready for accelerator and transport line installation.

(3) The transport line has been designed and fabricated. Now it is being assembled. By November 1, 1996, it should be installed in the facility.

(4) The accelerator has not yet arrived from AccSys Technology Inc. In order to expedite the delivery of the accelerator, technical personnel were sent to AccSys Technology Inc, California. The expected arrival date for the RFQ is November 26, 1996.

In view of the delay of the accelerator, it was decided to do some experiments on the Tandem Van De Graaff. We have run beam on a test target, and have 30 sets of data for five different geometries at three energies.

The data is now being analyzed. Figures 1 and 2 show the measured spectra from thick and thin Lithium targets at 2 and 2.2 MeV respectively.

Further experiments at some outside facility may be needed to complete the neutron measurements. For target engineering tests the Chemistry RFQ-DTL will still be used.

LDRD FUNDING:

FY 1996	\$ 188,449
FY 1997 (est.)	\$ 412,000
FY 1998 (est.)	\$ 200,000

Fig. 1. Measured spectra from thick and thin Li targets at E_p 2.2 MeV.

Fig. 2. Measured spectra from thick and thin Li targets at E_p 2.2 MeV.

LABORATORY DIRECTED RESEARCH AND DEVELOPMENT
1997 PROPOSED PROGRAM*

*New projects authorized for funding as of October 1, 1996.

Project Number 97-02

Physics Goals for a New Intense Muon Facility

W. J. Marciano

"An intense low energy muon beam facility at the AGS is envisioned to exploit and help further develop muon collider technology but would primarily be used to advance its own forefront physics program."

FY 1997 Funding \$95,000

Project Number 97-08

A Novel Curved Proportional Counter for X-ray Powder Diffraction Studies at NSLS

D. P. Siddons

G. C. Smith

"This proposal addresses the needs of x-ray powder diffractionists at NSLS and other synchrotron radiation sources. This technology has significant advantages over the current curved-detector technology, insofar as it promises increased counting rate and good energy resolution."

FY 1997 Funding \$95,000

Project Number 97-13

Extraction Kicker R&D for Target Shock Testing

A. J. McNerney

"The project will produce the design of a fastkicker magnet and pulse for the AGS. It shall be capable of extracting variable length, high-intensity beam pulses at high efficiency."

FY 1997 \$100,000

Project Number 97-16

Plasma Window for Transmission of Synchrotron Radiation

A. Herschovitch

E. D. Johnson

P. M. Stefan

"The development of the plasma window for synchrotron radiation applications could have an important impact on both the NSLS and other Light Source facilities around the world. Attenuation and spacial structure which attend the use of conventional window materials, represent a significant problem for various applications in synchrotron radiation research."

FY 1997 Funding \$60,000

Project Number 97-29

Development of New Techniques in Picosecond Pulse Radiolysis

J. F. Wishart

"The research would assist in the construction of time-resolved femto- and picosecond excitation and detection systems which unite the capabilities of pulse radiolysis with flash photolysis, and use the system to investigate the excited-state chemistry of radical species, charge recombination in hydrocarbons, and reactions of highly excited species."

FY 1997 Funding \$105,000

Project Number 97-39

X-ray Circular Dichroism of Biological Macromolecules

J. C. Sutherland

E. D. Johnson

C. C. Kao

"These experiments will determine which CD/MCD experiments are most promising for structural biology and what capabilities should be included in a dedicated facility. They are also necessary to give us an opportunity to learn the experimental methods required for x-ray spectroscopy."

FY 1997 \$96,000

Project Number 97-41

**Designing a Liquid Hydrogen Moderator
of Improved Performance for the High
Flux Beam Reactor**

J. D. Axe

"In this thimble it is proposed to place a moderator of re-entrant design in which the liquid hydrogen forms a few centimeter thick spherical shell."

FY 1997 Funding \$32,000

Project Number 97-44

X-ray Schlieren Computed Tomography

F. A. Dilmanian

L. D. Chapman

B. A. Dowd

D. P. Siddons

W. C. Thomlinson

"We propose to carry out x-ray schlieren imaging (XSI) in the tomographic configuration at the NSLS."

FY 1997 Funding \$59,000

Project Number 97-45

**Biodistribution Toxicity & Boron
Neutron-Capture Therapy in Animals
Using a Metallotetracarboranyporphyrin
Imageable by SPECT**

M. Miura

"The purpose of this proposed work is to synthesize new polycarboranyl porphyrins that are imageable by SPECT or MRI that have more favorable tumor uptake and better tumor:brain and tumor:blood kinetics than that of p-boronphenylalanine (BPA)."

FY 1997 Funding \$88,000

Project Number 97-50

**Development of Pump-&-Probe LIDAR
for the In-Situ Study of Fast Atmospheric
Chemical Reactions**

A. J. Sedlacek

"The goal of this LDRD proposal is to conduct in-situ study of fast atmospheric chemical reactions by performing a flash photolysis experiment in the troposphere using a new technique called Pump-and-Probe LIDAR."

FY 1997 Funding \$100,000

Project Number 97-70

**Molecular Biological Markers as
Potential Prognostic Indicators for BNCT**

J. Capala

J. Coderre

A. Chanana

A. Diaz

D. Joel

"We propose to do a pilot study to quantitate biological markers in tumor sections from BNCT-treated patients and to correlate these results with clinical outcome."

FY 1997 Funding \$100,000