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PROGRESS REPORT - 1985

CANCER RADIOIMMUNOTHERAPY: DEVELOPMENT OF AN EFFECTIVE APPROACH

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DEPARTMENT OF ENERGY GRANT

CANCER RADIOIMMUNOTHERAPY: DEVELOPMENT OF AN EFFECTIVE APPROACH

Sally J. DeNardo, M.D., Principal Investigator

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INTRODUCTION

The objective of this program is the development of effective approaches for delivering radiation therapy to patients with cancer using radiopharmaceuticals produced from monoclonal antibodies.

Three years ago we initiated this program with the support of the Department of Energy. We have followed our initial research plan as originally proposed and laid the groundwork in the areas of radionuclide selection, radiochemistry development, monoclonal antibody production, immunoglobulin immunochemistry, in vivo quantitative kinetics methodology and kinetic modeling. During this time greater than 40 publications and 30 presentations have been produced from the work directly supported by this grant. In 1984, the Society of Nuclear Medicine awarded the Berson-Yalow Award to the paper, "Perifusional Techniques for Screening Antibodies (Ab) in Living Tissues" authored by Gerald L. DeNardo, Andrew W. Saxe, Sally J. DeNardo, Alan Epstein, and Cathy Suey and presented by Dr. Gerald DeNardo. Development of scientific information concerning relative reactivities of monoclonal antibodies against human antigens are being further pursued by this methodology, and it is also being utilized as a key method of evaluating various linkages between the antibody and the metal chelate moiety which have been designed to improve the clearance of non-specific antibody uptake.

Another major achievement of this program has been the development of a new, Cu-67 chelator (Teta). This chelator firmly holds copper even in the presence of competitive serum proteins. Copper has proven to be labile with other chelators.

Under this program, Dr. Macey, in his first year with us, has developed a calibration phantom to be used when imaging patients in order to obtain absolute quantitation of the radionuclide uptake by SPECT. During this same period, Dr. Adams has demonstrated the capability of monitoring human lymphoma radioimmunotherapy in nude mice by the TMR quantitation of phosphate metabolites.

A single photon emission tomographic camera was purchased with University and philanthropic funds specifically for this program. This allows full-time developmental work on quantitative imaging approaches and in vivo kinetics of our various radiopharmaceutical antibody products. The pharmacokinetics of I-123 antibody and antibody fragments have been obtained in patients utilizing quantitative imaging and have demonstrated significant differences as well as the need for long-term studies with I-131 and Cu-67.

During this period three graduate students have finished their degrees. Two postdoctoral fellows have completed their training programs and assumed faculty positions, one with us and one at the University of Texas. These are enumerated on the following page. Noteworthy is,

however, Dr. Zanelli's Ph.D. thesis work, which was entirely funded by this program, on actual microdosimetry measurements of discrete low-energy electron point sources (Appendix I). This work provides actual measurements of low range energy deposition which documents the energy deposition calculations we made. These calculations were used for the radionuclide selections we have made, and will be used in the future for further nuclide selection.

Finally, a publication embodying our conceptual basis for obtaining quantitative pharmacokinetics in vivo for radiopharmaceuticals and their associated radiation dosimetry has been accepted for the special February, 1985 issue of the International Journal of Oncology, Biology and Physics, which has been dedicated in memorium of Dr. Henry Kaplan, a world renowned radiotherapist.

Our progress in the last three years has allowed us to assemble a team of people capable of addressing the specific problems that must be solved in order to develop radioimmunotherapy. Information derived from our work has allowed us to define the specific aims that need to be addressed to achieve radiation therapy using radiopharmaceuticals developed from monoclonal antibodies. The ongoing support from the Department of Energy is critical at this time in order to continue this developmental work.

In the first two-and-one-half years of this DOE Program, these individuals completed degrees or postdoctoral fellowship programs.

1. Claudio Zanelli: Received Ph.D. degree in Physics (thesis enclosed, Appendix I).
2. William Cole, Ph.D.: Finished postdoctoral fellowship with us under DOE (chelation chemistry for effective monoclonal antibody labeling). He now has a faculty position at University of Texas.
3. Dorothy Adams, Ph.D.: Finished postdoctoral fellowship under this program. (NMR evaluation of tumors receiving radioimmunotherapy). She now has a faculty position in this program at the University of California, Davis.
4. Kitty Chelton: Received Master's degree in Biophysics under this program.
5. Mario Avila: Received Master's degree in Radiochemistry with support of this program. (Ruthenium and Rhodium)

Ongoing Graduate Students and Postdoctoral Students

1. S. V. Deshpande, Ph.D.: Copper chemist who has just started his postdoctoral fellowship with us on Cu-67 monoclonal antibody labeling and metabolic ramification of variations chelate attachments.
2. David Fregeau: Ph.D. candidate in Immunology under the DOE program. (Biodistribution and metabolism of radioiodinated antibodies)
3. Min Moi: Ph.D. program in chelation Chemistry (see TETA papers).
4. Kiyoshi Koizumi, M.D.: Fellowship in kinetic modeling.

Pages 4 thru 10 intentionally omitted.

I. Explanatory Personnel Budget

	<u>Time %</u>	<u>Salary %</u>	<u>Salary</u>	<u>Benefits</u>
Sally DeNardo, M.D., Principal Investigator	30	5	\$ 2,000	\$ 480
Gerald DeNardo, M.D., Co-Principal Investigator	30	3	2,000	480
Lois O'Grady, M.D., Professor of Medicine, Oncologist/Hematologist	20	3	2,000	480
<u>Radiochemistry/Pharmacokinetics</u>				
Claude Meares, Ph.D., Professor of Chemistry; chelation chemist; will directly supervise Mr. McCall in producing bifunctional chelates, and graduate student, Mr. Moi, in designing and making new linkages.	25	-	-	-
Michael McCall, M.S., Organic chemist; will produce CITC, BABE, and new analogues with the linkages developed by Meares and Moi.	25	25	8,750	135
Min Moi, M.S., Graduate student; Ph.D. candidate in chemistry. Developed Teta. Will develop and evaluate new linkage analogues of CITC, BABE and TETA.	100	50	8,890	88
S. V. Deshpande, Ph.D., Radiopharmaceutical science, 1st year post doctoral fellow; Ph.D. background in copper chemistry and biochemistry; will be responsible for Cu-67 radiolabeling and biodistribution studies of various copper radiolabeled linkages, biochemical and radioautographic analysis of Cu-67-antibody metabolism, computer model implementation of mouse data.	80	80	17,683	4,244
David Fregeau, M.S., Ph.D. candidate in immunology under Dr. Sally DeNardo, Dr. Robert Scibienski and Dr. Kent Erickson. Will carry cell culture clones for all monoclonal lines, carry mouse models, complete his study of the biodistribution of radioiodinated antibodies by studying the cellular delivery using histology, light autoradiography and EM autoradiography.	100	50	8,890	88

	<u>Time %</u>	<u>Salary %</u>	<u>Salary</u>	<u>Benefits</u>
Harold O'Brien, Ph.D., Consultant/ collaborator from Los Alamos; will produce and purify Cu-67; will develop methods of radiolabeling our antibodies with Br-77. We have taught his people radioassay and protein chemistry tech- niques so that radiolabeling quality control can be done on Br-77-MAB at Los Alamos and so that they can understand the purity needs we have for Cu-67 antibody labeling.			Supported through Los Alamos	

SPECT Tomographic Quantitation/Patient Pharmacokinetics

Jo-Sen Peng, M.S., radioimmunochemist; radiolabels antibody and antibody fragments for <u>in vitro</u> perfusion and animal studies; produces enzyme-digested antibody fragments; biochemical and immunological quality control of radio- labeled molecules; animal distribution, biokinetics and tumor uptake; pyrogen and sterility testing.	100	100	24,677	7,156
Daniel Macey, Ph.D., Assistant Research Professor, SPECT tomographic physicist, responsible for SPECT quantitation development, new algorithms, patient target organ and tumor quantitation data for kinetic studies.	100	100	43,500	10,440
Stanley Mills, Ph.D., Radiopharmacist; radiolabels antibodies and fragments in the patient radiopharmacy using I-123, I-131, and when timely, Cu-67 for patient radiopharmaceuticals.	20	20	8,628	2,551
Dorothy Adams, Ph.D., biophysics, NMR technologist; assist in NMR analysis of therapy trials <u>in vivo</u> with I-131 and Cu-67.	25	25	6,450	1,548
Cathy Suey, Nuclear Medicine Technician; Radioassays of labeled antibodies; SPECT quantitative imaging of phantoms and patients; performs <u>in vitro</u> perfusion studies of antibody against human samples.	100	100	22,940	6,552
Barbara Amberson, Radiopharmaceutical Computer Technician; enters kinetic data, keeps record.	25	25	4,564	71
Total			\$ 160,972	\$ 34,313

Consultants

Marvin Goldman, Ph.D., Radiobiology, U.C. Davis
 Robert Scibienski, Ph.D., Immunologist, U.C. Davis
 Thomas Budinger, M.D., Ph.D., Physician biophysicist, tomographic physicist,
 U.C. Berkeley
 Manuel Lagunas-Solar, Ph.D., Hot Atom Chemist, U.C. Davis
 Kent Erickson, Ph.D., Histologist/cell biologist, U.C. Davis

II. Supplies

Radioisotopes: 1) Beam time for Hg-197 and Ru-97	\$ 2,000
2) I-125 for antibody human tissue <u>in vitro</u> perifusion studies and mice distribution studies	500
3) In-111 for studies in mice and human distribution studies	1,000
4) I-131 for therapy in mice and people mice 10 mCi x 5 people 20 mCi x 20 \$10-15/mCi 50 mCi x 3	4,500
5) I-123 \$25 x mCi/8 mc per labeling dose per patient kinetic study	2,000
No charge for Cu-67 from Los Alamos per Dr. Harold O'Brien	
Cu-67 shipping charges only for lead pigs both ways	350
Cu-67 from Brookhaven - no defined price yet until production method is in place and tested. Approximate \$20 per mCi may be necessary after that.	
Animal Purchase and Maintenance: Nude mice purchase = \$15/mouse @ 40/mo x 8 mo.	5,500
Chemical Reagents including cell culture supplies labeling supplies, glassware	5,000
Laboratory cost for 20 CBC and chem panels in feasibility studies	2,000
Column packing for HPLC (\$700/Column x 5 changes/yr)	<u>3,500</u>

\$26,350

III. Miscellaneous

Travel: 2 trips @ \$900 to present scientific data	\$ 1,800
Publication costs	500
Computer/camera maintenance contract (60%) (Siemens)	14,824
NMR time for tumor therapy evaluation (UCD/NMR facility)	<u>3,000</u>

\$20,124

IV. Equipment

Liquid nitrogen storage tank - increased capacity needed for secure storage of various monoclonal hybrid lines, tumor model lines, and cell lines necessary for controls in radioassays	2,000
Image table upgrade (see page 14)	<u>8,000</u>

\$10,000

EQUIPMENT JUSTIFICATION

Request to Upgrade Present SPECT Couch

Our current Siemens SPECT system acquires SPECT images with a fixed circular orbit over 360°. For areas of the body such as the abdomen, thorax and upper chest, which are more elliptical in outline, many of the images acquired with a circular orbit suffer from degraded resolution associated with comparatively large camera to patient distances. Some manufacturers offer systems now that allow elliptical orbit rotation for their gamma cameras. An alternative recently offered by General Electric Medical Systems is a moving SPECT couch that can simulate non-circular orbit acquisition for any SPECT camera system. Unlike true elliptical orbit rotation, this moving SPECT couch keeps the center of rotation at a fixed point in the section coordinate system.

Proven advantages of non-circular orbit SPECT are improved spatial resolution (~2 to 3 mm in 15 mm fwhm) for transverse section images, relaxed non-uniformity requirements that relate to the performance of present day cameras (~5%) compared with the values required for circular orbit rotation (~1%). Finally, the improved contrast offered by non-circular SPECT rotation has been shown to reduce the noise in transverse section images.

Funds requested: \$8,000.

BUDGET TOTALS

Personnel	Salaries	\$160,972
	Benefits	34,313
Supplies		26,350
Miscellaneous		20,124
Equipment		<u>10,000</u>
Total Direct Costs		\$251,759
Less Equipment		<u>10,000</u>
		\$241,759
Overhead (39%)		94,286
Total Direct Costs		\$251,759
Plus Overhead		<u>94,286</u>
Total Costs for Year 4		<u><u>\$346,045</u></u>

TOTAL COSTS FOR YEARS 4, 5 AND 6

Year 4   \$ 346,045

Year 5   \$ 366,208

Year 6   \$ 387,581

Total   \$1099,834

Years 05 and 06 reflect a 6% cost of living
for salaries and supplies.

Contact originator for omitted
information

END

**DATE
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4/9/92

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