Progress Report: Grant # DE-FG02-92ER60407 4 August 1992

**IMPROVING CANCER TREATMENT WITH CYCLOTRON PRODUCED RADIONUCLIDES**

Steven M. Larson, M.D. PI.; Ronald D. Finn, Ph.D. Co-PI.

Memorial Sloan-Kettering Cancer Center,
Nuclear Medicine Service S212C
1275 York Avenue
New York, New York 10021

212-639-7373 (Office)
212-717-3263 (FAX)

DOE/ER/60407--7

DE92 040310

**Introduction:**

OVERALL OBJECTIVE/RELATIONSHIP TO DOE'S PROGRAM/GENERAL PLAN AND APPROACH: This renewal application pursues our continuing long term goal of promoting nuclear medicine applications by **improving the scientific basis for tumor diagnosis, treatment and treatment follow-up based on the use of cyclotron produced radiotracers in oncology.** This program fits into the nuclear medicine component of the DOE mission, which is aimed at enhancing the beneficial applications of radiation, radionuclides, and stable isotopes in the diagnosis, study and treatment of human diseases. This program is administered within the Medical Applications and Biophysical Component of the Office of Health and Environmental Research, Office of Energy Research, DOE.

The grant includes 3 interactive components: Radiochemistry /Cyclotron; Pharmacology; and Immunology. An essential strategy is as follows: novel radionuclides and radiotracers developed in the Radiochemistry/Cyclotron section under the DOE grant during the 1989-1992 grant period, will be employed in the Pharmacology and Immunology sections of the DOE grant during the 1992-1995 grant period. The development of novel radionuclides and tracers is of course useful in and of itself, but their utility is greatly enhanced by the interaction with the immunology and pharmacology components of the program. In addition to its primary research mission, this project also provides a basis for training of research scientists in radiochemistry, immunology and bioengineering.

A DOE review, coordinated by the Office of Program Analysis, Office of Energy Research of this MSKCC DOE grant took place in Los Angeles in April 21-22, 1992. In this review, we were asked to emphasize "the scientific methods, recent progress, current project activities, and near-term research directions on your current contract or grant. Deviations, if any, from your original project task statement should be explained". The result of the review was strongly positive.

MASTER

**1. MAIN RESEARCH ACCOMPLISHMENTS OF THE LAST GRANT PERIOD 1989-1992**

During the grant period to date (4 August 1992), there have been 19 published papers, 2 Master's theses and 1 PhD thesis; 1 patent application; 2 papers in press; 2 papers submitted and 10 abstracts based directly on work supported by this grant. (See Bibliography)

Project 1. **Radiochemistry/Cyclotron: Innovations in target design and radiochemistry (R. Finn, PI).**

A. Original Objectives- **Development of novel I-124, and Ga-66 targets, as well as methods of radiolabeling to antibodies, and production on "baby" cyclotrons; development of novel targets for radiolabeled precursors; radiolabeling of anti-tumor drugs, including FUDR, methotrexate, and the cross-resistant drug colchicine, for studies of multi-drug resistance in animal and human tumors.** Enzymatic methods of labeling of amino acids and thymidine, which were included in the original grant have been set aside for the time being, in favor **development of IUDR as a substitute for thymidine, in assessing proliferative rates in vivo.**

B. Radiochemistry/Cyclotron Research Accomplishments

1. Refurbishment of CS-15 cyclotron, with replacement of outmoded control panels and targetry. Production of "routine" radiopharmaceuticals such as FDG, O-15 H2O.

The cyclotron was just barely operational at the beginning of this grant period, but is now fully functional (4 particles) with many modern improvements. FDG and O-15 H2O is now routinely available for clinical research programs supported by other funding, and in support of specific animal research supported by the DOE grant

2. Synthesis of radiotracers for drugs important in tumor pharmacology and multidrug resistance. (C-11 methotrexate, colchicine; F-18 FUDR)

Production methods of FUDR, along with characterization of chemical composition of the precursors has been accomplished, in support of drug retention studies which are now completed in a demonstration project in patients. The C11 target system is being installed, and the basic organic chemistry for production of C-11 methotrexate, C-11 Colchicine, has been accomplished. These drugs will be utilized in a series of experiments that will permit improved correlation of clinical resistance of tumors with the pharmacology and biodistribution of these clinically important drugs.

3. Production of novel radionuclides for immunology research (Iodine-124, Gallium-66)

Physical parameters necessary for production of these radionuclides measured, and a novel solid target designed. Availability of these

radioisotopes will lead to improved production methods of these interesting radionuclides with potential as labels for antibody research and immunotherapy.

4. Synthesis of radioiodinated IUDR (I125, I131), and the development of unique methods of production that greatly enhance shelf life of the radiolabeled reagent.

Production of IUDR for animal studies, and clinical demonstration projects (see below under "Pharmacology").

5. Radiolabeling of monoclonal antibodies A33,M195,3F8 with Iodine 124 for animal and human demonstration studies.

Technical features of radiolabeling with this radioisotope have been worked out which gives good yields and immunoreactivity of final products.

6. Radiolabeling of antibody 3F8 with Tc99m using a modification of the Schwarz method.

Reduction of disulfide bonds and the development of rapid approaches to Tc99m labeling of an important antibody with potential for use in neuroblastoma and small cell lung cancer.

Project 2. Pharmacology **(S.M. Larson, PI; B. Mehta, Co-PI; J. Biedler, R. Blasberg and J. Bertino, Consultants).**

a. A novel method for assessing multi-drug resistance in vivo

b. Assessing anti-tumor to chemotherapy agents based on assessment of DNA metabolism with radiotracers

c. Retention of antimetabolite in tissue in relationship to anti-tumor effects.

A. Original Objectives - Kinetic studies with long lived radiotracers (H-3 and C-14) in multi-resistant and sensitive animal tumors of a variety of types will be pursued to develop an appropriate "cross-resistant" drug that can serve as a marker substance for the demonstration of the multi-drug resistant phenotype in vivo. When the appropriate marker drug has been successfully radiolabeled with a positron emitter (our initial candidate is the drug colchicine), studies will be pursued in animals with PET imaging and if successful a demonstration project in humans is anticipated. Results of the radioactivity from the marker drug will be correlated with the quantitative expression of P-glycoprotein, using an unique antibody. Since many antitumor drugs act by interfering with DNA metabolism, a component of the original grant was directed toward the use of metabolic tracers in assessing tumor proliferation. Initially, a project was planned to evaluate the use of C-11 thymidine obtained by enzymatic labeling,

but because other groups already had a sizeable program in this area, our direction was changed to pursue the use of IUDR, as a radiotracer for DNA synthesis. In addition, FUDR, an antimetabolite drug which is used extensively in cancer treatment, particularly for colorectal cancer of the liver was proposed for studies in a limited series of patients with colorectal cancer using a specially designed gamma camera system, to assess retention of the drug in tumor versus liver.

B. Pharmacology Research Accomplishments

1. Demonstration of multidrug resistance based on less retention of radiolabeled colchicine in resistant in comparison to sensitive tumors.

Initial "proof of principle" studies have been completed and published, using H-3 Colchicine, and the studies repeated with C-14 colchicine using C-14 colchicine labeled in the same position as the C-11 compound, showing identical results. An extensive metabolite analysis, in plasma and tumor has been completed, with the C-14 compound that will serve as a basis for developing a modeling approach based on PET. Multidrug resistance is thought to be a major mechanism of clinical tumor resistance in patients. Techniques which could detect MDR in tumors, and monitor the effects of strategies that will reverse this, could have a major impact on treatment strategies.

2. Preliminary animal and human studies with radioiodinated IUDR demonstrate the possibility that PET and SPECT imaging in humans may be used as a basis for monitoring DNA synthesis.

We have demonstrated that IUDR is taken up and retained within DNA in an animal tumor model system. Although the uptake is less than thymidine labeled with C14 at the 3 position in the purine ring, the possibility of labeling with longer lived radioiodine isotopes that could be used for either SPECT or PET imaging led us to pursue this. Animal studies performed in Dr. Blasberg's laboratory at MSKCC demonstrated that uptake was greatest in the most rapidly proliferating tumors, and also, that more than 95% of total tumor radioactivity at 24 hours was retained in DNA, with the only other metabolite being free Iodide. This could simplify modeling kinetics for metabolic imaging methods based on PET or quantitative SPECT. Another important potential advantage, especially for brain tumors, is that since IUDR has increased lipophilicity, it has better penetration (3 to 4 fold) into brain than thymidine itself. This will be an advantage, particularly for brain tumors. Initial SPECT studies in humans using Iodine-131 IUDR, performed at MSKCC show the feasibility of early (4 hr) and delayed (24 hr) imaging of brain tumors.

3. Pharmacokinetics studies in humans with metastatic colorectal cancer of [F-18]FUDR tumor uptake after intra-arterial injection,

suggest strategies for improving tumor uptake and retention of the drug.

The uptake and transport of FUDR, an antimetabolite anticancer drug used in colorectal cancer, was rate limiting in the majority of patients with colorectal cancer metastatic to the liver. Five patients, 4 with colorectal cancer received injections of high specific activity FUDR (Xcuries/mg). The FUDR that was taken up into the tumors, was retained, but the amount taken up varied and was limited by the initial transport step from blood to tumor. Four of the 5 patients responded, 2 PR, 2 MR and the fifth had stable disease. The number of patients is too small to draw meaningful conclusions about the correlation between levels of tumor uptake and response, since all of the patients had at least some apparent drug effect, but the new finding that transport may be rate limiting in the final concentration of FUDR in tumor is important. This suggests certain strategies to increase uptake, based on actually slowing the flow of blood through the tumor, may permit more uptake and retention. Increasing blood flow to the tumor is unlikely to increase FUDR localization substantially.

Project 3. Immunology: **Quantitative immunokinetics and dosimetry of anti-tumor antibodies. (Keith Pentlow, Martin Graham, Farhad Daghighian and Gene DiResta, Project Leaders).**

A. Original Objectives- Positron emitting radionuclides with complex decay schemes, such as I-124 and Ga-66, have not figured prominently in applications to anti-tumor antibody dosimetry despite the obvious advantages of positron emission tomography for quantification. The reasons relate to concern about the ability to quantitatively image such radionuclides because of potential interference from time coordinated gamma rays that could fall in the time coincident window at an energy which would allow them to be detected as a coincident event. In a series of phantom studies, we propose to demonstrate that quantitative imaging of I-124 and Ga-66 is possible under conditions likely to pertain in vivo, for "hot-spot" imaging of tumors after parenteral injection. The purpose of this series of projects is to thoroughly evaluate the imaging physics of detection and quantification of I-124 and Ga-66 like radionuclides with modern PET scanners, and to extend the application to animal studies using a unique antibody system, radiolabeled 3F8, an antibody against neuroblastoma tumor. These observations in animals would lay the foundation for quantitative dosimetry of radiolabeled anti-tumor antibodies. In addition, it is likely that animal studies would be pursued with other antibodies, such as A-33, an anti-colon carcinoma antibody, and MX35, an anti-ovarian antibody. In addition, limited patient studies may be done (imaging and immunokinetic studies only). Also, some studies on the physiology of antibody localization will be undertaken.

B. Immunology Research Accomplishments

1. Physics of Positron Emission Tomography Imaging of Iodine-124

Iodine-124, despite a complicated decay scheme that includes only 25% positron decay, can be reliably imaged and quantitated with PET cameras of a variety of designs, even in the presence of large quantities of Iodine-131.

2. Development of mathematical models to analyze the physiology of penetration of anti-tumor antibody into tumor deposits in vivo.

3. Development of analytical techniques to experimentally verify for the first time the essential features of the Baxter-Jain hypothesis, which describes a variety of physical factors that can impede the transport of radiolabeled antibody into the center of tumor masses.

4. An artificial lymphatic system (ALS) has been developed and its function described in a mathematical model, an extension of the Baxter-Jain hypothesis, which is able to predict experimentally determined effects of mechanically changing interstitial fluid pressure in experimental animal tumors.

The experimental studies have been performed with a nude rat tumor model that is suitable for PET imaging studies. These systems have the potential for practical application in settings such as brain tumors, and possibly liver tumors, where reducing interstitial pressure in the center of tumors could substantially increase penetration and uptake of cytotoxic radiolabeled antibodies.

5. Development of pharmacokinetics models for antibody localizing to human tumor in vivo.

Optimizing dose and timing of dose to improve response of human tumors may result. An important feature of this model, was to incorporate the effects of the vastly different volumes of distribution of antibody and antigen into computations regarding the pharmacology of the distribution of radiolabeled antibodies in vivo.

6. Demonstration of feasibility of Iodine-124 labeled antibody as a method for improved estimates of radiation absorbed dose during radioimmunotherapy.

A child was studied with Iodine-124 labeled 3F8 antibody and the radiation absorbed dose computed from direct measurements using PET. This was the initial application of PET to an individual estimate of radiation absorbed dose for the purpose of radioimmunotherapy.

7. A mathematical model for immunokinetics of anti-tumor antibody in human brain tumors with emphasis on implications for microdosimetry of radioimmunotherapy.

Improvements in knowledge about basic immunology of penetration of antibody into tumors, as well as improved radioimmunotherapy.

**2. PLANS FOR CONTINUATION OF PRESENT OBJECTIVES AND NEW OBJECTIVES FOR GRANT PERIOD 1992-1995**

Project 1. **Cyclotron Innovations in target design and radiochemistry (R. Finn, PI).**

Original Objectives- **Development of novel I-124, and Ga-66 targets, as well as methods of radiolabeling to antibodies, and production on "baby" cyclotrons; development of novel targets for radiolabeled precursors; radiolabeling of anti-tumor drugs, including FUDR, methotrexate, and the cross-resistant drug colchicine, for studies of multi-drug resistance in animal and human tumors.** Enzymatic methods of labeling of amino acids and thymidine, which were included in the original grant have been set aside for the time being, in favor **development of IUDR as a substitute for thymidine, in assessing proliferative rates in vivo.**

Planned Continuation of Objectives: Development of rapid methods for radiolabeling of monoclonal antibodies with Iodine-124 will continue, and production methods in collaboration with Brookhaven will be finalized, based on enriched Te-124 as a target. Also, the development of the solid target system for the MSKCC Cyclotron, based on alpha particles on Sb, will permit production of I-124 on site in Manhattan, a very important step for solidifying the supply of I-124 for the future studies. Based on preliminary work developed under DOE 1989-1992, Gallium-66 will also be produced using the solid target system. Based on the biologic successes with IUDR, Iodine-124 will also be incorporated into IUDR, for quantitative PET studies of tumor proliferation. In addition, we will pursue more conventional radionuclides including Tc-99m and potentially, Rhenium isotopes. 3F8 has been successfully labeled with Tc-99m, using a modification of the Schwarz method, and Re labeled therapeutic formulations will be assessed, in collaboration with Dr. Lynn Francesconi of Hunter College. Synthesis of C-11 methotrexate and colchicine are scheduled for completion by the end of the current grant period(1989-1992). For labeled methotrexate and for colchicine the non-radioactive precursors (N-(4-[[2,4 diamino-6-pteridinyl methyl]amino-benzoyl]glutamic acid and colchicine, respectively), have been successfully synthesized, and with the availability of the high activity $^{11}C$ target system, which is being implemented now in the third year of our current grant cycle, radiolabeled drugs will be produced for animal studies, to begin in mid year. Once these compounds have been completed, work will begin on the development of other antimetabolite which show some clinical promise, in order to create a radiotracer for pharmacology studies. The synthesis of 5-fluoro-2-deoxyuridine based on the reaction of acetylhypofluorite with 2'deoxyuridine has been successfully completed, so no additional chemistry development is planned for this compound. Both Ga-66 production by alpha

bombardment of a copper target, and the I-124 production by proton bombardment of enriched Te-124 target have shown promise in initial studies and these will be continued, in order to create I-124 for the biologic and physical science studies planned under project 3.

Project 2. Pharmacology **(S.M. Larson, PI; B. Mehta, Co-PI; J. Biedler, and J. Bertino, Consultants).**

a. A novel method for assessing multi-drug resistance in vivo

b. Retention of antimetabolite in tissue in relationship to anti-tumor effects.

c. c. Preliminary assessment of radioiodinated iododeoxyuridine (IUDR) for assay of DNA synthetic rates in vivo.

**Hypothesis 1: Tumor retention and anti-tumor effect are highly correlated for certain anti-cancer drugs; i.e. anti-metabolites and biologically derived drugs affected by the multidrug phenotype.**

**Hypothesis 2: Uptake and retention of IUDR in human tumor may be used as an indication of DNA synthetic rate. In preliminary studies, uptake will be sufficient for adequate quantitative assessment using PET and SPECT in brain tumors, and at 24 hours, the large majority of tumor contained radioactivity will be in the DNA fraction.**

Original Objectives - Kinetic studies with long-lived radiotracers (H-3 and C-14) in multi-resistant and sensitive animal tumors of a variety of types will be pursued to develop an appropriate "cross-resistant" drug that can serve as a marker substance for the demonstration of the multi-drug resistant phenotype in vivo. When the appropriate marker drug has been successfully radiolabeled with a positron emitter (our initial candidate is the drug colchicine), studies will be pursued in animals with PET imaging and if successful a demonstration project in humans is anticipated. Results of the radioactivity from the marker drug will be correlated with the quantitative expression of P-glycoprotein, using an unique antibody. Limited patient studies with [F-18]-FUDR will be pursued to assess the role of uptake and retention in the anti-tumor response of colorectal cancers, metastatic to liver, A specially designed gamma camera will be used for these studies.

Planned Continuation of Present Objectives: Having established the basic principal of increased uptake of cross-resistant drugs in the more sensitive cell lines, and decreased uptake in the resistant lines, we will refine the analysis of retention to determine the effect of verapamil and the monoclonal antibody on this retention, and to determine the effect of such action on improving animal survival for certain drugs which are active against the target tumors chosen, including adriamycin and vincristine. Our basic study plan will employ sensitive and resistant neuroblastoma cell

lines, and in addition to using $^{14}$C-labeled tracers and biodistribution studies, as soon as the $^{11}$C-colchicine is available, animal studies will be performed with the PC4600 PET scanner, to determine the parameters of detection of MDR sensitive versus resistant tumors, by quantitative imaging of labeled drug retention in tumors versus normal tissues. Depending on the magnitude of uptake of colchicine uptake in tumors, and the metabolite pattern, we will evaluate the possibility of developing formal PET modeling approaches to quantitate transport into tumors using PET. A limited number of patient demonstration studies will be employed, most likely in a patient study currently under may using Recent studies with MRK16 antibody have shown promise for detecting the presence of the P-glycoprotein on the tumor cells, and parallel studies will be performed with I-125 or I-124 MRK as a way of detecting resistant tumors, in comparison to the colchicine methodology.

Using the newly developed antimetabolite tracer drug C-11 methotrexate, we will pursue the correlation of retention of drug in tumors, with anti-tumor results, and the role that a radiotracer could have in predicting response of these tumors to therapy. These radiotracer studies are based on the recent work of one of our consultants, Dr. J. Bertino, whose recent studies with a series of anti-metabolites including methotrexate have shown that the development of tumor resistance occurs when tumors no longer retain high drug concentrations.

IUDR has been developed by the radiochemistry group, and initial studies performed by Dr. R. Blasberg, our consultant indicates that the biology is favorable for use of this tracer to assess DNA synthetic rate, particularly in brain tumors, but possibly in lung tumors as well. Serious questions remain, however, about whether enough IUDR will be taken up to permit statistically accurate quantitative imaging, either with SPECT(I-131,I123) or PET(I124). We will do limited patient demonstration studies to assess this.

Project 3. **Quantitative immunokinetics and dosimetry of anti-tumor antibodies. (K. Pentlow, M. Graham, Farhad Daghighian and Gene DiResta, Project Leaders).**

Hypothesis 1: Quantitative imaging approaches with PET will lead to non-invasive methods for improved dosimetry and immunokinetics for radioimmunotherapy.

Hypothesis 2: Increased antigen expression by tumors and reduced central pressure in tumor masses will lead to improved localization of antibodies for radioimmunotherapy.

Original Objectives- Positron emitting radionuclides with complex decay schemes, such as I-124 and Ga-66, have not figured prominently in applications to anti-tumor antibody dosimetry despite the obvious advantages of positron emission tomography for quantification. The reasons relate to concern about the ability to

quantitatively image such radionuclides because of potential interference from time coordinated gamma rays that could fall in the time coincident window at an energy which would allow them to be detected as a coincident event. In a series of phantom studies, we propose to demonstrate that quantitative imaging of I-124 and Ga-66 is possible under conditions likely to pertain in vivo, for "hot-spot" imaging of tumors after parenteral injection. The purpose of this series of projects is to thoroughly evaluate the imaging physics of detection and quantification of I-124 and Ga-66 like radionuclides with modern PET scanners, and to extend the application to animal studies using a unique antibody system, radiolabeled 3F8, an antibody against neuroblastoma tumor. These observations in animals would lay the foundation for quantitative dosimetry of radiolabeled anti-tumor antibodies. In addition, it is likely that animal studies would be pursued with other antibodies, such as A-33, an anti-colon carcinoma antibody, and MX35, an anti-ovarian antibody. In addition, limited patient studies may be done (imaging and immunokinetic studies only). Also, some studies on the physiology of antibody localization will be undertaken.

Planned Continuation and New **Objectives**

**a) to thoroughly evaluate the imaging physics of detection and quantification of I-124 and Ga-66 like radionuclides with modern PET scanners.**

b) **to determine tumor physiology which is important to tumor localization, and if possible provide approaches which will lead to improved uptake of radiolabeled antibody.**

c) **to perform animal studies and limited patient demonstration studies to validate the concept that quantitative imaging with PET can be used to more accurately measure radiation absorbed dose (macro and micro-dosimetry) and immunokinetics of tumor targeting.**

Imaging physics studies performed under DOE 1989 to 1992 have conclusively demonstrated for all of the diverse PET systems so far studied (6 distinct designs) , that I-124 can be quantitatively imaged, even in the presence of large quantities, up to 100 times greater, of I-131. In two in-vivo animal tumor systems, namely, nude mice bearing neuroblastoma tumors, and nude rats bearing human ovarian cancer, the ability to measure concentrations of radiolabeled antibody in vivo has been validated. Having established the quantitative nature of imaging with positron emitting radiolabeled antibodies, in the initial grant period, and having developed quantitative models for immunokinetics that permit estimates of microdose from auger emitting forms of Iodine, such as Iodine 125,124,123, we propose studies to validate these concepts of radiation dosimetry in animal model systems, predominantly nude rats bearing NMB7 neuroblastoma tumor. In addition, we have developed a quantitative autoradiographic system, for detailed study of microdistribution in tumors in animals, as a basis for

improving the understanding of tissue factors that influence uptake, particularly the relationship of antigen expression to tumor uptake. This system will also make it possible to evaluate microscopic antigen distribution is tumors, and will also be valuable in assessing local microdistribution of dose, and its impact on. We propose further refinement of these methods to assess the role of antigen expression to determining tumor localizations of 3F8 antibody. IL4 is said to stimulate GD2 antigen expression in neuroblastoma tumors, and we will assess the impact of IL4 in terms of effects on both antigen expression and uptake. The NMB7 tumor system in nude mice, shows a sharp decline in uptake of the antibody with increasing size of tumor, and detailed studies may give insight into the mechanisms of these changes. Recent progress in assessing the impact of tissue pressure an mechanical factors on antibody localization have come from the work of this DOE grant, and further studies are planned to validate a mathematical model which describes the impedance to inflow of antibody into the region of the tumor. Furthermore, a system for reducing the interstitial pressure within tumors has also been developed, to assess the Baxter-Jain hypothesis. These studies will be pursued in parallel, to determine to what extent the tumor localization of 3F8 antibody into animal tumors can be improved. In addition, it is likely that animal studies would be pursued with other antibodies, such as A-33, an anti-colon carcinoma antibody, and antigen binding peptides that react with TAG-72 antigen. In addition, limited patient studies may be done (imaging and immunokinetic studies only), in patients with brain tumor, colorectal and pediatric tumors, as limited demonstration of the principles developed in the animal model systems.

**3. GRADUATE STUDENTS TRAINED:**

Masters Degree Granted

a. **Osama Malawi, M.S.** Bioengineering (Nuclear Medicine Research Laboratory) Maintain PC4600 PET camera and the coincidence detector apparatus; acquire and analyze the H2015 and F18DG studies in animals using the coincidence detector apparatus

b. **Jongbin Lee, M.S.**, Ph.D. Bioengineering. Design, build and implant ALS probes and pumps into tumor bearing animals; fabrication of WIN and CLGH probes; data acquisition and analysis of IFP, IFV and MoAb ALS animal data.

Post-Doctoral Tenure

a. **Vipa Bookitticharon, Ph.D.** (International Atomic Agency Fellow) Technetium-99m labeling of 3F8 monoclonal antibody

b. **Diu-Thu Vo, M.D.**, Post-doctoral fellow QAR methodologies and laboratory research on targeting of radioimmunotherapy Factors important in the localization of radioiodinated 3F8 to NMB7 neuroblastoma in vivo.

Ph.D. Degree Granted

a. **Jongbin Lee, M.S.**, Ph.D. Bioengineering

Ph.D. Candidates

a. **Osama Malawa, M.S.**, Bioengineering at Columbia University (see above)

b. **Sunil Konath, B.S.**, Chemical Engineering; Bioengineering Program, Columbia University (Start date Sept. 1992) Conduct doctoral dissertation research in Nuclear Medicine Research Lab: responsible for developing the mathematical analysis and software necessary for multiple ALS placement.

c. **Ravi Moorthy, M.S.**, Chemical Engineering; Bioengineering Program, Columbia University (Start date July 15, 1992) Conduct doctoral dissertation research in neurosurgical research lab: responsible for tumor propagation; conduct the autoradiographic studies to determine the effects of ALS on MoAb uptake; measure tumor Ph and $pO_2$ before and after ALS intervention; prepare animals for FDG studies.

(Edward Leonard, Ph.D., Professor of Chemical Engineering, Chairman, Bioengineering Program, Columbia University.)

## 4. BIBLIOGRAPHY


1. Cooper AJL, Nieves E, Filc-DeRicco S, Gelbard AS. Short-term metabolic fate of [13N] ammonia, L-[13N] alanine, l-[13N]glutamate and L-[amide-13N] glutamine in normal rat liver in vivo. (Awarded first prize as best paper by the Dutch Academy of Liver Disease). Proceedings 6th International Symposium on Ammonia Metabolism. Maastricht, The Netherlands, April 27-29, 1987. Advances in ammonia metabolism and hepatic encephalopathy. PB Soeters, JHP Wilson, AJ Meijer and E. Hold, eds. pp 11-25, Elsevier Science Publisher 1988.

2. Conlon KC, Bading JR, DiResta GR, Corbally MT, Gelbard AS, Brennan MF. Validation of transport measurements in skeletal muscle with N-13 amino acids using a rabbit isolated hindlimb model. Life Sci 1989;44:847-859.

3. Arbit E, Di Resta GR, Bedford RF, Shah NK, Galicich JH. Intraoperative measurement of cerebral and tumor blood flow with Laser-Doppler flowmetry. Neurosurgery 1989; 24:166-170.

4. Calderon J, Cooper AJL, Gelbard AS, Mora J. 13N isotope studies of glutamine assimilation pathways in neurospora crassa. J Bacteriology 1989;171:1771-1774.

5. Thesis by Osama R. Mawlawi. A Coincidence Detection System for the Measurement of uptake of Positron Labeled Compounds.Polytechnic University, Bioengineering 12/17/1990,

6. Gelbard AS, Cooper AJL, Asano Y, Nieves E, Filc-DeRicco S, Rosenspire KC. Methods for the enzymatic synthesis of tyrosine and phenylalanine labeled with nitrogen-13. Int J Radiat Appl Instr Part A.1990;41:229-233.

7. Filc-DeRicco S, Gelbard AS, Cooper AJL, Rosenspire KC, Nieves E. Short-term metabolic fate of L-($^{13}$N) Glutamate in the walker 256 carcinosarcoma in vivo. Cancer Res 1990;50:4839-4844.

8. Finn RD, Tirelli S, Sheh Y, Knott A, Gelbard AS, Larson SM. Consequences of electroplated targets on radiopharmaceutical preparations. Nucl Instrum Methods in Physics Research 1991; B56/57:1284-1286.

9. Sordillo PP, DiResta GR, Fissekis J, Conti P, Benua RS, Yeh SDJ, Laughlin JS. Tumor imaging with carbon-11 labeled alpha-aminoisobutyric acid (AIB) in patients with malignant melanoma. Amer J of Physiologic Imaging 1991;6:172-175.

10. Finn RD, Cheung NKV, Divgi C, St. Germain J, Graham M, Pentlow K, Larson SM. Technical challenges associated with the radiolabeling of monoclonal antibodies utilizing short-lived

positron emitting radionuclides. Nucl Med Biol 1991; Vol 18,No.1: 9-13.

11. Finn RD, Boothe TE. Quality assurance considerations related to "in house" radiopharmaceutical preparations using positron emitting radionuclides. In:Emran A, Ed. New Trends in Radiopharmaceutical Syntheses, Quality Control and Regulations. Plenum Press, NY 1991;399-407.

12. Pentlow KS, Graham MC, Lambrecht RM, Cheung NKV, Larson SM. Quantitative imaging of I-124 using positron emission tomography with applications to radioimmunodiagnosis and radioimmunotherapy. Med Phys 1991;18(3):357-366.

13. Fissekis JD, Nielsen CM, Tirelli S, Knott AF, Dahl JR. A remote control process for the routine synthesis of branched chain [1-$^{11}$C]-alpha amino acids. Int J Radiat Appl Instrum Part A 1991; Vol 42, No.12: 1169-1176.

14. Van Leeuwen PAM, Bading JR, Vydelinqum NA, Younes RN, DeRooij P, Brennan MF. Organ blood flow in Fischer-34 rats bearing MCA-induced sarcoma. J Appl Physiol 1991;71:1674-1687.

15. DiResta GR, Lee J, Arbit E. Measurement of brain tissue specific gravity using pycnometry. J Neuroscience Methods 1991;39:245-251.

16. Mehta BM, Rosa E, Fissekis JD, Bading JR, Biedler JL, Larson SM. In vivo identification of multidrug resistance with radiolabeled colchicine, a potential agent for positron emission tomography. J Nucl Med 1992;33:1373-1377.

17. Mulshine JL, Shuke N, Carrasquillo J, Daghighian F, Ghosh B, Walsh T, Avis I, Reynolds JC, Cuttitta F, Larson SM. The correct dose: Pharmacologically guided end point for anti-growth factor therapy. Cancer Research (Suppl) 1992; 52:2743s-2746s.

18. Cheung N-KV, Pentlow KS, Graham MC, Yeh SJ, Finn RD, Larson S. Radiation absorbed dose and tumor response during therapy with 3F8 Iodine-131 conjugated monoclonal antibody. In: Watson EE, Schlafke-Stelson AT, eds. Fifth International Radiopharmaceutical Dosimetry Symposium (CONF-910529). Proceedings of a conference held at Oak Ridge, Tennessee; Oak Ridge Associated Universities, 1992: 95-112.

19. Daghighian F, Pentlow KS, Larson SM, Graham MC, DiResta GR, Yeh SDJ, Macapinlac H, Finn RD, Arbit E, Cheung N-K V. Application of PET and compartmental modeling in estimation of cellular level microdosimetry: PET studies of I-124 labeled 3F8 MAb in human glioma. In: Watson EE, Schlafke-Stelson AT, eds: Fifth International Radiopharmaceutical Dosimetry

Symposium (CONF-910529). Proceedings of a conference held at Oak Ridge, Tennessee: Oak Ridge Associated Universities, 1992: 396-413.

**Articles in Press**

1. Larson SM, Pentlow KS, Volkow ND, Wolf AP, Finn RD, Lambrecht RM, Graham MC, DiResta G, Augenson F, Malawi O, Bendriem B, Daghighian F, Yeh SDJ, Wang GJ, Kalaigian H, Cheung NKV. PET scanning of $^{124}$I-3F8 as a novel method of tumor dosimetry during treatment planning for radioimmunotherapy in a child with neuroblastoma. (J Nucl Med 1992).

2. Conlon KC, Bading JR McDermott EWM, Corbally MT, Talvo AJ, Brennan MF. Extremity metabolism in the cachectic, VX-2 carcinoma-bearing rabbit. (J of Surgical Research 1992)

**Thesis**

1. Mawlawi OR. (Masters) A coincidence detection system for the measurement of uptake of positron labeled compounds. Polytechnic University, Bioengineering 12/17/90.

2. Lee J. (Masters) Development of pycnometer method for measuring water content in rat brain tissue. Polytechnic University, Bioengineering 1990.

3. Lee J. (Ph.D.) Characterization of parameters affecting macromolecular transport in neuroblastoma xenograft. Polytechnic University, Bioengineering 1992.

**Submitted:**

1. Bading JR. A method for analytic estimation of solute transport and distribution volume parameters. (Submitted to Am J Physiol, Modeling Methodology Forum, 10/1/91).

2. Daghighian F, Pentlow KS, Larson SM, Graham MC, DiResta GR, Yeh SDJ, Macapinlac H, Finn RD, Arbit E, Cheung NK. Development of a method to measure kinetics of radiolabeled monoclonal antibody in human tumor and applications to microdosimetry: PET studies of I-124 labeled 3F8 MAb in glioma. (Submitted to Eur J Nucl Med 7/92)

**Abstracts Published:**

1. Pentlow KS, Graham MC, Lambrecht RM, Larson SM. Quantitative imaging of radiolabelled antibodies using positron emission tomography. Medical Physics 1989; 16:676.

2. Pentlow KS, Graham MC, Lambrecht RM, Larson SM. Quantitative imaging with Iodine-124 and positron emission tomography. Radiology 1989; 173 (P): 191.

3. Kairemo KJA, Daghighian F, Brownell A-L, Rubin SC, Federici M, Pentlow KS, Larson SM. Positron emission tomography (PET) for diagnosis of ovarian cancer metastases using I-124 labeled monoclonal antibody in a nude rat model. J Nucl Med 1990;31765.

4. Kairemo KJA, Daghighian F, Brownell A-L, Rubin SC, Federics M, Pentlow KS, Larson SM. Positron emission tomography (PET) for diagnosis of cancer metastases using I-124 labeled monoclonal antibody in a nude rat model. Eur J Nucl Med 1990; 16:S54.

5. Pentlow KS, Graham MC, Daghighian F, Finn R, Bacharach S, Bendriem B, Robeson W, Lambrecht R, Larson SM. The use of positron emission tomography for quantitative imaging of I-124 labelled antibodies. J Nucl Med 1990; 31:864.

6. Pentlow KS, Graham MC, Cheung NKV, Lambrecht RM, Finn R, Larson SM. Quantitative imaging of I-124 labelled antibodies using positron emission tomography. Eur J Nucl Med 1990; 16:S55.

7. Daghighian F, Kairemo KJA, Rubin SC, Federici M, Larson SM. Intraoperative beta probe for detecting tumor deposits using I-131 and I-124 labeled monoclonal antibodies (MOAB). Eur J Nucl Med 1990; 16:S53.

8. Daghighian F, Pentlow KS, Larson SM, DiResta GR, Graham MC, Yeh SDJ, Macapinlac H, Finn RD, Arbit E, Cheung NKV. Development of a method for quantitative measurement of the in vivo kinetics of radiolabeled antibody in human tumor: PET studies of I-124 labeled 3F8 monoclonal antibody in human glioma. J Cereb Blood Flow Metab. 1991; 11:S397.

9. Daghighian F, Pentlow KS, Larson SM, DiResta GR, Graham MC, Yeh SDJ, Macapinlac H, Finn RD, Arbit E, Cheung NKV. In vivo kinetics of radiolabeled antibody: PET studies of I-124 labeled 3F8 MAB in human glioma. J Nucl Med 1991; 32:1021.

10. Graham MC, Scheinberg DA, Daghighian F, Pentlow KS, Liu G, Divgi C, Capitelli P, Larson SM. Preliminary dosimetric experience with I-131 M195 monoclonal antibody in acute myelogenous leukemia. In: Watson EE, Schlafke-Stelson AT, eds: Fifth International Radiopharmaceutical Dosimetry Symposium (CONF-910529). Proceedings of a conference held at Oak Ridge, Tennessee: Oak Ridge Associated Universities, 1992:482.

**Patents**

DiResta G, Lee J, Arbit E. **United States Letters Patent**
Process and device to reduce interstitial fluid pressure in tissue.
Submitted April 1992 (patent pending)

**5. OPINION STATEMENT REGARDING STATE OF KNOWLEDGE REGARDING CYCLOTRON PRODUCED RADIOTRACERS IN ONCOLOGY FOR PHARMACOLOGY AND IMMUNOLOGY; ITS SIGNIFICANCE AND NEEDED FUTURE INVESTIGATIONS.**

Cancer research initiatives of the 50's, 60's and 70's have found their way into the everyday oncology practice of the 80' and 90's. The Atomic Energy Agency and its direct descendant, the Department of Energy, have supported nuclear medicine research heavily and we owe much of modern day nuclear medicine practice to this support: the development of Technetium-99m, the modern gamma camera, Single Photon Tomography, Positron Emission Tomography, are examples of such DOE support. Also, when the "War on Cancer" was declared by President Nixon in 1972, and the National Cancer Institute was established, research initiatives were begun which have resulted in major impact on clinical care in the United States and throughout the world. (3). The use of mammography for screening breast cancer patients, combination chemotherapy for many common cancers, the biotechnology revolution, were prompted by NCI/NIH support. Now more than ever, modern nuclear medicine techniques are being widely applied in oncology for diagnosis and therapy of malignant tumors. Diagnostic nuclear medicine techniques contribute to the clinical care of the cancer patient by 1) detecting the presence of occult tumors; 2) staging tumor extent 3) monitoring the response of tumors to therapy. 4) assessing the impact of tumors on normal organ and tissue physiology. Therapeutic nuclear medicine is useful in the curative and palliative therapy of a growing number of tumor types, and in the control of symptoms resulting from cancer, as in the control of cancer pain.

DOE will have an important role in the future in the providing essential support for basic nuclear medicine research that will be translated into clinical practice in the year 2000 and after. This research support will be targeted to growth opportunities in

1) **instrumentation research,** especially computerized imaging modalities like PET and SPECT. The areas of promise here include applications of computers to image analysis, to "fuse" MRI and nuclear medicine images, and for the purposes of dosimetry of radiotracers targeting cancer for the purposes of therapy. This is a major area of need just now, and quantitative imaging approaches such as are discussed in this grant will help establish essential dose response relationships. Also, better hardware is needed and new detector systems for PET, such as Lutetium based detectors, should lead to improved resolution and sensitivity. Cyclotron research and development to improve ease of use of these extremely valuable research instruments must continue to be supported by DOE, in order that novel radiotracers will continue to be developed as a basis for biomedical advances in numerous areas of medical science.

2) **the "new biology"**-especially molecular engineering and genetics research. Novel radiolabeled antibodies and related molecules,

receptor binding ligands, improved sites for radiotracer attachment, created by genetic engineering are all feasible projects that if given support could provide major payback in improved health care.

3) **Radiochemistry and new radiotracer development**-new ways of radiolabeling of biomolecules, more rapid production of cyclotron produced radionuclides and their use in radiolabeling and for diagnosis and therapy. Also, there is a tremendous need to improve knowledge about the bioavailability and concentration of anti-cancer drugs and biologic response modifiers in tumors, in order to better understand the phenomenon of dose response relationships and the underlying mechanisms of resistance of cancers to these therapies. The success of **gene therapy**, which seems so promising, may in the end depend on the ability to target adequate quantities of DNA to the right spot within the cell. Radiotracers will aid greatly in this process, and the DOE should support such efforts.

# END

DATE
FILMED
11 / 2 / 92