DOE/ER/60407--1

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IMPROVING CANCER TREATMENT WITH CYCLOTRON PRODUCED RADIONUCLIDES

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February 1, 1992-July 15, 1995

COMPREHENSIVE PROGRESS REPORT
DE-FG02-86ER60407

DISCLAIMER

Progress Report: Grant # DE-FG02-86ER60407 17 July 1995

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Introduction:

OVERALL OBJECTIVE/RELATIONSHIP TO DOE'S PROGRAM/GENERAL PLAN AND APPROACH: The accompanying renewal application continues our long term goals 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 DOE's 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/Immunology; and Imaging Physics. An essential strategy is as follows: novel radionuclides and radiotracers developed in the Radiochemistry/Section under the DOE grant during the 1992-1995 will be employed in the Pharmacology/Immunology component in the period 1996-1999. Imaging Physics resolves relevant imaging related physics issues that arise during the experimentation that results. In addition to our basic research mission, this project also provides a basis for training of research scientists in radiochemistry, immunology, bioengineering and imaging physics.

1. MAIN RESEARCH ACCOMPLISHMENTS OF THE GRANT PERIOD (1992-1995.)

During the total grant period to date (1989-1995) there have been a total of 46 (25 in 1992-1995) publications; 5 master theses and 1 PhD thesis (3 master thesis in 1992-1995); 2 patent

applications (1 patent in 1992-1995); 5 articles and book chapters in press; (1992-1995); and 40 abstracts (30 in 1992-1995). (See Bibliography).

In the grant period of 1992 to 1995, the Radiochemistry/Cyclotron group developed novel radionuclides(Ga-66, I-124) for labeling of antibodies, and also radiotracers for the study of multidrug resistance(such as C-11 Colchicine) and tumor cell proliferation (such as labeled Iododeoxyuridine, (IUdR, and a series of F-18 labeled nucleosides)). The CS-15, 4 particle cyclotron, upgraded in the 1989-1992 grant period, performed to expectations. The Pharmacology/Immunology group studied the MDR phenotype, relating resistance to the quantitative expression of p-glycoprotein. Initial studies with radiolabeled IUdR demonstrated proof of principle for assessing tumor cell proliferation *in vivo*, as well as an initial indication of therapeutic potential. The only significant problem which was disruptive of planned work in the grant period of 1992-1995, was the delay in construction of the PET facility, so that some of the planned PET imaging physics projects were delayed. Because of this equipment problem, the major emphasis of the physics group shifted to developing and improving more conventional SPECT and planar gamma camera dosimetry methods. Dosimetry methodology was developed for the radiolabeled antibody program, for which patient trials were supported by a number of NIH grants. This resulted in considerable progress in the dosimetry of radiolabeled antibodies targeting to tumors. Work also began on the imaging physics of tumor detection by Single Photon Emission Tomography (SPECT). Recently, working with phantoms at a nearby site, initial work was finished on the physics of Ga-66 PET imaging. Finally, the ADVANCE Whole Body GE PET scanner will be delivered in the 1st week of August, 1995. This machine will add considerably to the research capabilities of our program.

Project 1. Project 1. Radiochemistry/Cyclotron: Innovations in target design and radiochemistry (R. Finn, Project Leader; Y. Sheh, V. Bui, P. Kothari, S. Cai).

A. **Original Objectives** - Development of a novel solid target system appropriate for utilization on "baby" cyclotrons and the production of unique radionuclides in support of the immunology program including gallium-66, iodine-124 and rhenium-186; development of novel targets for the preparation of synthetic precursors; radiolabeling of anti-tumor drugs, including colchicine and iodo-deoxyuridine for studies of multi-drug resistance in animal and human tumors and assessment of rates of tumor proliferation *in vivo*, respectively.

B. **Radiochemistry/Cyclotron Core Facility Research Accomplishments**

1. Development of a novel solid target system and production of unique radionuclides in support of the immunology program.

The refurbishment of the cyclotron at Memorial Sloan-Kettering Cancer Center accomplished in the previous grant period included the installation of a state-of-the-art target changer and chilled helium foil cooling recirculation system. At the time of installation, the manufacturer did not have a designed cyclotron target to allow the irradiation of either solids or powders. Our efforts were directed toward the fabrication of an external target whose dimensions were dictated by the

constraints of the auto target changer. Moreover, the target system envisioned was to address several potential scenarios, i.e. to handle powder as well as electroplated targets, to allow the reuse of the target header assembly, to provide target alignment with the beam at a grazing incidence angle, and to operate either under chilled helium foil cooling or in vacuum.

The fabricated solid/powder target unit was specifically designed to fit the MSKCC Japan Steel Works Ltd. automatic target changer and to allow irradiation of materials both with and without foil cooling. Its design allows the remote removal of the reusable target head and requires application of minimal target material to achieve thick target yields with low energy cyclotrons. Consideration of intrinsic radionuclide activation was an important component in the target material choices for the target header and backing plates. The target unit has successfully operated with all four particles available at MSKCC CS-15 cyclotron, although at restricted beam currents. Further experiments to evaluate the thermal performance of the current design with various target backings at elevated beam currents available from the CS-15 is requested in our renewal application.

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

Physical parameters necessary for the production of the radionuclides have been measured utilizing the solid target unit previously described. In addition to the measurement of the cross section for the production of iodine-124 from the irradiation of an enriched elemental tellurium target with energetic deuteron particles, alternative nuclear reactions were evaluated using both protons and alpha particles incident upon enriched tellurium and antimony, respectively. The 15 MeV alpha particle available at MSKCC cyclotron and experiments on the Duke University cyclotron also conducted at 15 MeV, indicated that the published cross section for this nuclear reaction may require reevaluation. However, the proton irradiation of tellurium oxide at 15 MeV protons, holds promise for the production of iodine-124. Preliminary results indicate a production rate of approximately 400-500 uCi per uA-hr of iodine-124 with our accelerator. Work continues with the preparation of a platinum target blank containing enriched tellurium-124 as tellurium oxide. The technique necessary to prevent sublimation of the tellurium oxide target material has been evaluated and finalized using natural tellurium oxide.

The production of gallium-66 has been accomplished using alpha particle bombardment of electroplated copper targets. The target backing is elemental silver for efficient heat dissipation. In addition, the irradiation of natural zinc in powder form has been successfully employed to prepare gallium-66. The advantage of the zinc irradiation is with the elimination of a shorting bar change and returning of the cyclotron prior to bombardment. The chemical separation techniques are very similar for both processes.

We have reported the electroplating techniques applicable to cyclotron targetry using antimony and copper and the advantages of the solid/powder target unit in the scientific literature.

3. **The radiolabeling of anti-tumor drugs, i.e. colchicine-^{11}C.**

Kinetic studies utilizing long-lived radiotracers (^{3}H and ^{14}C) in -resistant and -sensitive animal tumors of a variety of types have indicated that the development of carbon-11 labeled n-colchicine would serve as an appropriate "cross-resistant" drug marker for the demonstration of the multi-drug resistant phenotype *in vivo*. The compound has been successfully synthesized along with isocolchicine in multi-millicurie concentrations. Utilizing a similar synthetic strategy, we also were able to synthesize milligram quantities of the carbon-13 enriched compounds and the magnetic resonance signal assignment for (-)-9-[^{13}C] isocolchicine was reported.

4. **Radiolabeling of monoclonal antibodies for animal and human demonstration studies.**

A series of technical difficulties associated with the radiolabeling of the radioisotopes of iodine, including iodine-124 and iodine-123, have been worked out and reasonable chemical yields and acceptable immunoreactivity of the final product formulation are obtained. The extension of the technique to include alpha emitting and beta emitting radionuclides such as bismuth-213 and yttrium-90 respectively, is continuing.

5. **Radiochemistry/Cyclotron Core Support for DOE Program Projects.**

In addition, the requirement for production of various short-lived radiopharmaceuticals/precursors required in support of the pharmacology and immunology project components is a responsibility of the Radiochemistry/Cyclotron Core group. The Radiochemistry/Cyclotron Core continues with the evaluation of synthetic routes for the preparation of various radiopharmaceuticals utilizing short-lived radionuclides available from the cyclotron. Included in this group of compounds are ^{18}F-FDG, ^{15}O-H_2O, $^{123,124}I$-IUdR, ^{18}F-FUdR, ^{18}F-FFAU, $^{131,123}I$-FIAU, and various monoclonal antibodies radiolabeled with cyclotron-produced radionuclides, MRK-16, HM-195, 3F8, and CC-49. As the proof of principle becomes established, the results of our efforts become a component of the pilot data submitted to various granting agencies for evaluation of continued clinical support.

C. **INDICATION OF CURRENT PROBLEMS OR FAVORABLE OR UNUSUAL DEVELOPMENTS.:** NONE

Project 2.A. Pharmacology

A. Original Research Objectives: Kinetic studies with long-lived radiotracers (H-3 and C-14) will be used in biodistribution studies, and as soon as C-11 colchicine is available, it will be used in PET studies and biodistribution studies to show equivalency with these longer lived agents. Studies with MRK16 antibody have show promise for detecting the presence of p-glycoprotein in tumor cells (qualitatively), and parallel studies will be performed with I-125 and I-124 MRK as a way of detecting resistant tumors, in comparison to the colchicine methodology for looking at functional capacity of tumors. Using the antimetabolite tracer drug C-11 methotrexate, we will pursue the study of correlation of retention of drug with anti-tumor effects, in collaboration with 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 concentration. IUdR has been developed by the radiochemistry group, and initial studies

performed by Dr. R. Blasberg, indicates that the biology is favorable for the use of this tracer to assess DNA synthetic rate, particularly in brain tumors. Serious questions remain, however, about whether enough IUdR will be taken up to permit statistically accurate quantitative imaging, either with SPECT (I-131, I-123) or PET (I-124) . We will do limited patient demonstration studies to assess this.

Multi-drug resistance(MDR) and p-glycoprotein (pGP)

1. Our earlier studies with ^{3}H- and ^{14}C-labeled Colchicine(CHC), showed the uptake of colchicine in Balb/c nude mice, xenografted with colchicine -sensitive BE(2)-C human neuroblastoma tumor to be greater than its corresponding -resistant BE(2)-C/CHCb tumor(1,2). It was important to ascertain that ^{11}C-CHC, when given to patients, will behave like ^{14}C-CHC. This was carried out by studying the distribution of ^{14}C-CHC using whole body Quantitative Autoradiography technique, since our ultimate aim is to produce ^{11}C-CHC for patient use.

2. ^{11}C-CHC has been synthesized in our laboratory by Kothari et al (3), and therefore the study of biodistribution of ^{11}C-CHC in colchicine -sensitive and -resistant tumors has to be carried out to compare the distribution of colchicine labeled with ^{3}H-, ^{14}C- and ^{11}C- radionuclides.

3. It has been shown that a membrane transport phosphoglycoprotein, p-glycoprotein (pGP) is frequently overexpressed in multidrug resistant tumor cells, and may be responsible for drug resistance through the efflux of hydrophobic antitumor drugs from the tumor cells (4,5). This is supported by the fact that compounds like verapamil (6), cyclosporine (7), and FK-506 (8), have been shown to reverse the multidrug resistance *in vitro*, by competitively inhibiting the binding of antitumor drugs to pGP and increasing the intracellular accumulation of antitumor drugs.

4. It has been observed that the resistant neuroblastoma cells BE(2)-C/CHCb (9) and others derived from the same parental sensitive cell line BE(2)-C (9), lose their resistance to the drug following removal of the constant pressure of the drug. Also tumor cells have been reported to lose MDR *in vivo* through reduced pGP expression in absence of the pressure of colchicine. Since the cells are maintained in presence of drug, there is a possibility that drug elimination can change the pGP expression and also the tumor grown in the animals, may not retain the same characteristics viz., the resistance level as well as the expression of pGP. We have decided to study MDR and pGP expression *in vitro* and *in vivo* without the pressure of colchicine, using labeled MRK-16.

5. Since uptake of Colchicine in resistant and sensitive tumors is dependent on the presence of MDR1 gene and ultimately its gene product p-glycoprotein (pGP), pGP expression was determined by the monoclonal antibody MRK-16 binding experiments. There were two aspects to be studied. First, by reacting with MRK-16 to measure the number of receptor sites and second by Western blot analyses to further confirm the findings.

6. The multiple cell lives of BE(2)C which have been made resistant to colchicine and other drugs of the MDR phenotype, express varying pGP concentration over a 60 fold range. We plan

to exploit this unique model system to study factors affecting uptake of radiolabeled antibody into tumors *in vivo*. In particular, the role of antigen density will be studied.

Studies of proliferation and therapy with I-131,I-125,I-123 IUdR

7. Produce radiolabeled IUdR suitable for human studies, labeled with a variety of isotopes of iodine. The agents are to be used in human studies, which are supported by NIH grants, and the initial trials are small scale pilot studies, designed to assess the proof of principle.

8. Provide phantom studies to aid in dose selection and feasibility for SPECT imaging with I-123 and I-131 in patients with human brain tumors, as well as analysis of kinetic data obtained from human trials in patients with brain tumors injected with I-131 or I-123 IUdR.

9. Provide dosimetric analysis of patient imaging data derived from patient studies performed with a combination of I-131/I-125-IUdR under NIH grant CA501CA61586-03 - "New Therapeutics for Hepatic Metastases from Colorectal Cancer", J. Bertino, PI.

B. Research Accomplishments of Project 2. Pharmacology

a) Quantitative studies with C-14 colchicine, labeled at the ring C-methoxy group, demonstrated increased uptake in sensitive(BE-2(C) in comparison to resistant tumors(BE-2(CHC). This was comparable to prior studies performed with H-3 colchicine, and demonstrated the potential usefulness of this tracer for *in vivo* monitoring of MDR phenotype.

b) Development of Quantitative Autoradiography methods for measuring the distribution labeled colchicine throughout the tissues of a tumored mouse. The average colchicine concentration in the sensitive tumor was 18.4 nMoles/gram versus 7.2 nMoles/gram in the resistant tumor, when corrected for metabolites, under the conditions of testing. The liver was the main metabolizing organ.

c) C-11 Colchicine was synthesized by the radiochemistry group and the uptake compared in the sensitive and resistant tumors of the mouse. Results agreed within experimental error to the prior studies with C-14 and H-3 colchicine, indicating that C-11 Colchicine could be used as a PET tracer for monitoring MDR phenotype *in vivo* in patients.

d) MRK-16, an antibody against external epitopes on the p-glycoprotein, the membrane transport protein responsible for the MDR phenotype, had higher uptake ($p<.05$), in resistant in comparison to sensitive xenografts in nude mice.

e) MRK-16 was used as the basis for quantitative methods for measuring the molar expression of resistant and sensitive cell lines growing in tissue culture. The assay was validated by comparison to Western blot techniques. The expression of p-glycoprotein is sensitive to the concentration of ambient colchicine in the medium of resistant cells, and within days, concentrations can change markedly with changes in ambient concentration of colchicine in the

medium. The induced changes in p-glycoprotein expression correlated well with changes in the sensitivity of the cells as measured by growth inhibition assays.

f) MRK-16 was used as a probe for QAR methodologies, and for sensitive and resistant tumors growing in nude mice. For the first time that we are aware, these techniques permit the direct measurement of p-glycoprotein in tissue sections on a molar basis. The degree of resistance of various cell inoculum, correlated closely with the molar expression of p-glycoprotein in tissue sections obtained from mouse tumor xenografts.

g) Mathematical models were developed of binding of radiolabeled antibody for *in vitro* assay of pGP on free cells growing in tissue culture and QAR measurement of pGP in tissue sections. This analysis permitted optimization that is appropriate to differing assay conditions in order to reduce error of measurement, and allow a systematic approach to correcting for varying immunoreactivity and non-specific binding and permit easy automation of data analysis.

h) In regard to the assessment of tumor cell proliferation with radiolabeled IUdR, phantom studies have demonstrated proof of principle that imaging with SPECT of patients with human brain tumors is feasible, for I-131 and I-125.

i) Initial human studies showed that the IUdR distribution in human gliomas was at the periphery of the tumor, beyond the rim of enhancement seen on MRI. This suggests that the growing region of the tumor is largely at the edge of the tumor, and may in fact be outside the usual treatment field for radiotherapy of even surgical extirpation. Although this has been suspected for some time based on pathologic evidence, our studies represent the initial indication of a potential diagnostic test that might be used to help improve planning of treatment ports or surgical approaches to control all of the proliferating region of human brain tumors.

j) Data analysis of initial human studies after intra-hepatic arterial injection of I-125/I-131 has been performed, using the I-131 as a tracer for I-125 for therapy of metastatic colorectal cancer. The studies showed that 5 mCi of I-125 was sufficient to deliver about 200 molecules of I-125 IUdR to each proliferating cell nucleus, and that the uptake was sufficient to kill cells in S-phase at the time of injection. In preliminary studies, injections repeated at intervals of 1 week, showed a highly reproducible uptake and clearance, and indicated that repeated injections at that interval would be equally effective in terms of tumor localization. An analysis of tumor control probability indicates that prolonged infusion of the tracer will be the most effective to kill tumor, with normal non-proliferating tissues likely to show little if any toxicity. These theoretical considerations will be used as a basis for planning of a therapeutic trial to be performed under CA5R01CA61586-03, J. Bertino, PI.

C. Indication of current problems or favorable or unusual developments: The availability of I-124 in sufficient quantities for patient studies was a limitation for PET studies, and also, we had only the PC4600 brain scanner during this period because of construction delays for our PET scanner. For this reason, we emphasized studies with conventional isotopes of iodine, and these studies were largely successful for proof of principle; i.e. for IUdR SPECT imaging for example.

In addition, there were unanticipated problems with C-11 methotrexate synthesis, and because of priority issues favoring the production of labeled IUdR, and other labeled nucleosides, we have switched our interest to Iodomethotrexate, an anti-metabolite which can be readily labeled with the iodine isotopes, tracers more suitable for long term study. This will be pursued further in the next grant period. Also, we have arranged for regular shipments of I-124 from the Royal Marsden in London. (Bimonthly, 10 mCi or more per batch).

D. Summary of Accomplishments: Methods have been developed and validated to measure the functional changes in tumor cells in terms of retention of radiolabeled MDR sensitive drugs suitable for use as a PET tracer in humans (C-11 colchicine). In addition, the level of p-glycoprotein can be measured either in tissue culture or tissue sections with MRK-16. Initial studies in animals indicate that labeled MRK-16 could potentially be used for qualitative monitoring of the expression of p-glycoprotein in human tumors *in vivo*. These methods will be powerful tools in the laboratory for the study of the MDR phenotype in a variety of human tumors and tissues, and may offer the opportunity to measure the function and relate this to the molar expression of p-glycoprotein both *in vitro* and *in vivo*. In regard to IUdR, formulations of proper specific activity, sterility and apyrogenicity have been used in human trials, which show the zone of proliferation of human gliomas *in vivo* to be at the extreme periphery of the tumors, well outside the zone normally treated by surgery or radiotherapy. Dosimetric analysis of human studies of I-125 IUdR, provide a basis for the planning of Phase I/II outpatient regimens for treating hepatic metastases of colorectal cancer, that have a high probability of tumor control, if careful clinical testing shows that the predictions of low toxicity for non-proliferating tissues is fulfilled.

Project 3. Immunology

Project 3A Quantitative immunokinetics and dosimetry of anti-tumor antibodies

A. Original Objectives: To thoroughly evaluate the imaging physics of detection and quantification of I-124 and Ga-66 like radionuclides with modern PET scanners. and 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. Quantitative imaging approaches with PET will be used in order to validate standard imaging approaches obtained through SPECT.

B. Research Accomplishments: We purchased a GE ADVANCE Scanner nearly 3 years ago, but because of problems associated with construction at our site in Manhattan we are just now (August 1995), preparing to receive delivery of this unit. For this reason, the emphasis was shifted away from PET imaging toward improving our more standard dosimetric methods. We believe that this approach had considerable success, both in terms of measuring kinetics of antibody localization to tumors, and also to lead to improved dosimetry for a number of radiolabeled antibody trials performed under several NIH grants developed here at the institution.

1. Partially supported by the DOE funding, was the development and application of the "3D-ID" dosimetric method. This method uses CT or MRI studies obtained from individual patients, along with SPECT or PET images. After the different modalities are registered with each other, they are provided as input to 3D-ID which uses the activity distribution from SPECT or PET to obtain a three-dimensional distribution of absorbed dose or dose rate that is then directly related to patient anatomy by superposition on the CT/MRI studies. This is done using a point-kernel technique that has been validated by comparison with MIRD S-factors. 3D-ID also provides as output dose-volume histograms which succinctly summarize the dose distribution within the target volume and which may be important in understanding biological effect.

2. Also partially supported by DOE funding was a detailed analysis of red marrow dosimetry, in particular the potentially errors associated with bone marrow biopsy. This analysis provided a theoretical derivation for the 0.2 to 0.4 blood to marrow activity concentration conversion factor for antibodies that do not specifically bind to marrow components. The work demonstrated that a value within this range may be derived from very basic principles requiring estimation of marrow extracellular space and distribution volume of the administered agent. The bone marrow biopsy analysis demonstrated that depending, upon processing of the biopsy, a significant understimulation of the marrow activity concentration may be made and that this might explain to some extent the highly variable results that have been obtained in animal experiments.

3. A plan for outpatient treatment of liver metastases using IUdR, delivered by intrahepatic infusion pump, has been developed. In developing this treatment strategy a number of factors were considered including tumor control probability, the potentially heterogeneous potential doubling time within a tumor cell population, administration schedule, and patient hazard both in terms of red marrow dose and allowable activity within the patient for release.

4. A technique has been developed and implemented in a small number of patients in which serial planar images are first registered and a pixel-by-pixel fit to an exponential expression is obtained. In this manner kinetic information is presented over the whole body as a single parametric image. This has provided an alternative approach to assessing patient kinetics and is free from the potential bias associated with selecting regions of interest for kinetic analysis (i.e., kinetic information is obtained over the whole-body, thereby potentially revealing unexpected regions of rapid uptake or clearance). Once each pixel has been fit to an exponential equation, images of the clearance rate, lambda; the intercept or time-zero activity level in each pixel and the cumulated activity may be obtained. The latter by performing an analytical integration for each pixel. The potential errors associated with counting statistics and image resolution have been examined and the technique has been found to provide valuable information both qualitative and quantitative.

5. Tumor dosimetry has been performed for 7 thyroid cancer patients, on 9 different dates. Three to four planar images following a 5 to 10 mCi dose of I-131 have been used to obtain pharmacokinetics for individual tumors. This information has been combined with CT to obtain tumor volumes. The calculated dose has been compared with patient response as measured from CT to establish a relationship between tumor dose and tumor response. There is a wide range of

dose rates from 3 rad/mCi I-131 to >900 rad/mCi. In general, tumor dose is directly proportional to the likelihood of response. Tumor dose is greatest for lymph nodes of the neck and soft-tissue uptake in lungs, and is lowest for uptake in bony lesions. This is similar to the historical response rates of neck nodes>> lung nodules>>bone disease. In addition, we have analyzed the radiation dose to tumor and normal tissues from a group of antibody patients treated with the antibody CC49. Tumor dose for 11 analyzable tumors was 7.1 mCi/rad on average. Red marrow dose is consistently in the range of approximately 1 rad/mCi for the initial injection, (1.4 rad/mCi, n=30); and then becomes much lower with subsequent injections(0.3 rad/mCi). A thorough analysis was performed of repeated injections in a patient with a complete response to radiolabeled antibody therapy alone (I-131 3F8), for a large chest wall lesions of neuroblastoma. A total of 376 mCi's in 6 divided doses were administered to a 3 year old child. Dose to red marrow was approximately 450 rads, and caused profound pancytopenia, which responded to autologous marrow infusion. Total tumor dose was 4900 rads.

6. Daghighian, Futimoto, and Zhang have developed and implemented a modification of the conjugate-view methodology. The modification involves using CT to sum the thicknesses of underlying and overlying tissue for a particular pixel of interest to obtain a pixel-by-pixel attenuation correction map which may then be used to correct the counts in a region-of-interest obtained from a planar study. The normal tissue radioactivity is estimated from an adjacent region. Phantoms studies show that this method is accurate to +/- 20% for tumors larger than 60 cc.

7. The Chen and Pelizzari method for fusing SPECT and CT images of the brain has been adapted to other body regions for use with a variety of tumor specific tracers including radiolabeled antibodies for both in the "3D-ID" program, and also for better evaluation of suspicious regions seen on CT or MRI scanning. To facilitate the fusion (Dr. Zhang and Daghighian) have developed a simple band that can be filled with radioactivity to give a well defined edge of the body on SPECT scanning. This method is invaluable when there is very high tumor specificity, as in the case of I-131 thyroid cancer imaging, and greatly speeds image fusion techniques.

8. The statistical noise involved in imaging of tumors with SPECT cannot be analytically calculated in most practical clinical situation, because the noise is spatially correlated due to the reconstruction methods employed. ("lumpy" background problem). In particular, this can cause false positive detection in low tumor to normal tissue ratio situations. For this reason we performed a series of phantom experiments using Tc-99m and I-131 to determine the limits of detection for a 3 cc tumor, the approximate volume of an enlarged lymph node. We studied the detection as a function of tumor/background ratio and the concentration of radioactivity in the tumor. At realistic concentrations for radiolabeled antibody targeting of tumors, we found that a 5:1 ratio was detectable for Tc-99m, and a 7:1 ratio for I-131.

9. Preliminary experiments, which were partially supported by the DOE, were performed to demonstrate as a proof of principle, the scintillating crystal lutetium oxyorthosilicate(LSO), as a detector for PET. The initial experiments showed that LSO had 5 times higher light output than

BGO, with comparable stopping power for 511 KeV photons. Furthermore, using LSO crystals and position sensitive PMT's we demonstrated that a high resolution image (1.5 mm) can be achieved in an animal PET scanner design.

C. INDICATION OF CURRENT PROBLEMS OR FAVORABLE AND UNUSUAL DEVELOPMENTS:

Memorial Sloan-Kettering Cancer Center has established a program in "Whole-Body PET Imaging". New space and facilities have been developed for our PET center, and initial installation of the GE ADVANCE whole body PET scanner, with adjacent biologic and computer support labs has begun, with a planned completion of Sept. 15, 1995. This will add greatly to our capabilities for high resolution PET imaging.

Project 3B: Enhancement of Monoclonal Antibody Delivery to Tumors using an Artificial Lymphatic System (G.R. DiResta, P.I.)

A. Original Objectives: The aim of this study was to evaluate the efficacy of an artificial lymphatic system (ALS) to reduce interstitial hypertension and enhance uptake of therapeutic agents. Three objectives were pursued: 1) Development of methodology to measure pertinent transport parameters 2) Characterization of IFP, IFV, pH, pO_2 and rGMR in the human neuroblastoma rat xenograft model and 3) Measure specific and non-specific monoclonal antibody (moab) uptake before and after IFP manipulation.

B. Research Accomplishments

1) Methods development

The development of methods to measure interstitial fluid pressure (IFP), and velocity (IFV) has been completed. IFP is measured using wick-in-needle (WIN) probes developed for rat and mouse tumors. The rat tumor probes were made from 26 gauge 316 stainless steel cannula and mouse tumor probes from 30 gauge 316 stainless steel cannula (A5). The probes were connected to a sensitive Camino optical pressure transducer. Position independent IFV probes were developed and used to measure the velocity profiles of rat tumors (P1). All pressure and velocity measures were recorded using our computerized data acquisition system. Data analysis utilized Baxter-Jain mathematical models and mathematical models which we derived.

All of our preliminary drug uptake studies were performed using an ALS system consisting of a vacuum pump with a single hole 18 gauge stainless steel cannula. This system represented the simplest system which could be used to test the ability of an ALS in a tumor. A closed form solution to the Baxter-Jain equations with a central sink as a second boundary condition was derived for this simple probe centrally placed within a tumor. Its experimental use required that the rodent be anesthetized. We determined that 30 minutes were required before IFP was reduced. Moab uptake "with ALS" sessions were typically 2 hours long, and were repeated every 24 hours for 3 days. We have recently developed a fully implantable ALS and are testing it in rodents. The system includes multi-hole-probes, a manifold and a vacuum pump. The

animal can now move about freely. A US Letters patent has been awarded for the ALS concept, and we've submitted a Continuation In Part patent application for the newest aspects of the ALS system. A manuscript to describe the ALS system and its associated mathematics is currently being reviewed (P3).

We have developed a dual tumor rodent model which we now routinely use to study impact of ALS on physiological parameters, and drug uptake. This model reduces the number of animals required by 50%; Each animal serves as its own control. One tumor receives the ALS while the other acts as a control.

2) Characterization of IFP, IFV, pO_2, pH and GMR in the human neuroblastoma rat xenograft model .

The measurement methodology developed in Phase 1 is routinely used in our laboratory. It has resulted in a publication (P1) which provides experimental evidence to support the Baxter-Jain mathematical model. Our experimental observations also showed that IFP profiles are tumor specific, a finding which was not anticipated by the mathematical model. Our methodology has also been used to measure IFP in rodent models used by Department of Surgery collaborators. We observed elevated IFP in their hepatic tumor model (A6) and most recently in a sarcoma model. Interstitial hypertension has been observed in every rat and mouse solid tumor we've measured. IFP ranged from 10 to 26 mmHg , while normal muscle IFP is -.4 mmHg.

In addition to our animal studies, we have applied our methodology to the characterization of IFP in human brain tumors. These measurements, made under an IRB approved protocol during surgery prior to resection, demonstrated that brain tumors also present interstitial hypertension. The average IFP observed from 22 studies was 6.7 mmHg; IFP ranged from 2 - 15 mmHg. Normal cortical values was .6 mmHg. Further, we observed a linear relationship between central tumor IFP and a brain edema index. This finding helps to explain the existence of edematous brain tissue surrounding tumors. The brain does not have a lymphatic system. Edema results when the rate of fluid extravasation from tumor capillaries exceeds the rate of percolation through the brain parenchyma. Interstitial fluid thus accumulates in normal regions surrounding the tumor. Brain edema index, derived from T2 weighted MRI images, provides a quantitative estimate of the extent of this edematous region. Manuscripts and abstracts describing our brain tumor findings have been published (P2;A1,2,3,4).

We have recently developed insertable pO_2 probes using the 30 gauge cannula to measure the tissue oxygen profiles in our rat neuroblastoma xenograft model. Tumor pO_2 profile measurements are underway and are expected to be completed by September.

Baseline glucose metabolic rates (GMR) have been measured in the rat neuroblastoma tumor model using ^{18}FDG with our coincidence detection apparatus. The GMR values agree with published values for rodent tumors. In addition, we've completed the pH profile measurements in our rodent model using miniature glass pH electrodes (Diamond Electrotech) and observed the

tissue pH to be acidic within its core, typically 6.4. These results will be included in a second characterization paper scheduled for submission when our pO_2 profiles are completed (P4).

3) Measure specific and non-specific moab uptake before and after IFP manipulation.

The impact of ALS on tumor IFP and flow have been performed using a single hole, single probe ALS placed within the center of our rat tumor. These studies clearly demonstrated that ALS reduced IFP within the vicinity of the probe and increased tumor blood flow. The Baxter-Jain equations were solved for the impact of the presence of an ALS probe. Numerical predictions agreed with the experimental IFP profile measurements. These experiments determined that multiple probes were needed to reduce IFP throughout the tumor, and that the influence of the ALS reduced the hydrodynamic impedance present within tumor. A manuscript (P3) has been submitted which presents these findings.

Preliminary rodent studies have been completed which demonstrate the effectiveness of ALS to increase uptake of specific and non-specific antibodies into tumors. We performed these studies using our simplest ALS probe with our dual flank tumor model. We examined the ability of ALS to increase uptake of 3F8 moab into the rat Walker 256 mammary carcinoma; The 3F8 was non-specific for this tumor line. We observed an increase of 37%. Two specific tumor uptake studies have been completed. We measured an increase of 67% for CC49 moab in a colorectal tumor, and 80% increase in 3F8 moab in neuroblastoma.

We have also demonstrated that an ALS can significantly increase the uptake of a small molecular weight drug, doxorubicin, into tumors. We observed a 25% increase of this drug in a rodent sarcoma tumor. We attribute this finding to the increased tumor blood flow which results when the tumor's interstitial hypertension is reduced. A manuscript, in preparation, summarizes our findings. (P5)

A mathematical model was developed to explore the impact of the acidic milieu we observed within tumors on the kinetics of the antigen-antibody reaction. The numerical simulations predicted that the reaction uptake would be reduced by ~50%. *In vitro* experimental studies have confirmed the sensitivity of the antibody-antigen reaction to pH. Animal studies are currently underway to evaluate impact of ALS on tumor pH profiles.

The effectiveness of ALS-enhanced drug uptake on tumor metabolism will be measured using ^{18}FDG PET. These studies will be conducted this fall after acceptance testing of our new GE ADVANCE PET scanner is completed. This decision was made because of the superior resolution of the ADVANCE (4 mm) over our current PC4600 PET(11 mm), and because our coincidence system utilizes a single pairs of detectors and thus is not suitable with the dual tumor model we now use.

C. Summary

The enhanced uptake of specific and non-specific macromolecules, and small molecular weight therapeutic agents following reduction of IFP is evidence which supports the Jain hypothesis that

interstitial hypertension is a major impediment to delivery and uptake of chemotherapy into tumors. Our preliminary findings have contributed to substantiating this theory by providing experimental verification. Our findings have also shown that hydrodynamic impedance is tumor specific and can be reduced using a mechanical artificial lymphatic system.

2.0 PLANS FOR CONTINUATION OF PRESENT OBJECTIVES AND NEW OBJECTIVES FOR GRANT PERIOD 1996-1999

Project 1. Cyclotron Innovations through Target Design and Radiochemistry (R. Finn, Project Leader).

A. **Original Objectives** - Development of a novel solid target system appropriate for utilization on "baby" cyclotrons and the production of unique radionuclides in support of the immunology program including gallium-66, iodine-124 and rhenium-186; development of novel targets for the preparation of synthetic precursors and radiolabeling of anti-tumor drugs, including colchicine and iodo-deoxyuridine for studies of multi-drug resistance in animal and human tumors and assessment of rates of tumor proliferation *in vivo*, respectively.

B. **Planned Continuation of Objectives**: Development of optimized methods for radiolabeling of monoclonal antibodies with iodine-124 as well as with various radiometals produced on the CS-15 cyclotron will continue. Although the collaboration with Brookhaven continues to be a rewarding effort, production of the various radionuclides "in-house" would be the most logical and efficient option to pursue. For example, time should be available upon the MSKCC cyclotron such that the proton irradiation of a tellurium oxide target and separation of the iodine by a dry distillation technique should allow the preparation of 10-20 millicurie quantities of this radionuclide. Naturally, the irradiations would be interrupted and extended over several days. The results of the investigation would continue to be shared with our colleagues at Brookhaven Cyclotron Facility. Gallium-66 will continue to be prepared on the CS-15 using the natural zinc target bombarded with 15 MeV protons. The production of unique PET radionuclides such as yttrium-86 from powdered strontium target material will also be studied. The investigations should demonstrate the capability of PET in support of diagnostic evaluation, dosimetry calculations directly applicable to therapeutic treatment utilizing yttrium-90 labeled monoclonal antibody CHX-DTPA-HuM-195 in the leukemia model.

Other radionuclides being evaluated include the preparation of ^{94,96}Tc and their respective metastable states, as well as rhenium-182,186. The similarity of chemistry but diversity in half-life between the technetium and rhenium radionuclides promises to provide an insight into the rapid radiolabeling of monoclonal antibodies. In addition our experience employing different chelates for radiometals will be extended and compared with the evaluation of photochemically induced intrinsic sulfide dative bonds and subsequent radiochemical labeling.

These results when considering the changing regulatory environment applicable to PET facilities and the required quality assurances of the various radiolabeled compounds/monoclonal antibodies should provide significant documentation into methods appropriate for radiopharmaceutical and radiobiologic compounds.

Based upon the biologic successes with IUdR, iodine-124 will be incorporated into this radiopharmaceutical for quantitative PET studies of tumor proliferation. In the past grant period, 3F8 was successfully radiolabeled with Tc-99m using a modification of the Schwarz method. Experience gained through this effort combined with the rapid internalization of HuM-195 will allow the performance of definitive studies on dosimetry to be accomplished using this radioiodinated monoclonal antibody. The radioiodinated monoclonal antibody will serve as a standard of comparison to the radiometal label antibodies previously mentioned.

Moreover, to provide an improved target system for the production of the aforementioned radionuclides, investigations with computer simulations for the evaluation of the thermal properties of the target materials and blanks followed by experimental verification of such computations, will be undertaken by the Cyclotron staff. Synthesis of carbon-11 labeled colchicine in both animal models and possibly, clinical trials should be achieved. Based upon current regulations, either PRC approval or IND submission will be required.

Efforts to prepare ^{14}O-H_2O as well as ^{15}O-H_2O should allow the Cyclotron Core the luxury of avoiding a particle change on the cyclotron and to improve efficiency of time utilization in those studies requiring blood flow measurements combined with other radiopharmaceuticals, i.e. colchicine/fluoro-deoxyglucose.

Project 2.A. Pharmacology

A. Original Research Objectives: Kinetic studies with long-lived radiotracers (H-3 and C-14) will be used in biodistribution studies, and as soon as C-11 colchicine is available, it will be used in PET studies and biodistribution studies to show equivalency with these longer lived agents. Studies with MRK16 antibody have show promise for detecting the presence of p-glycoprotein in tumor cells (qualitatively), and parallel studies will be performed with I-125 and I-124 MRK as a way of detecting resistant tumors, in comparison to the colchicine methodology for looking at functional capacity of tumors. Using the antimetabolite tracer drug C-11 methotrexate, we will pursue the correlation of retention of drug with anti-tumor effects, in collaboration with 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 concentration. IUdR has been developed by the radiochemistry group, and initial studies performed by Dr. R. Blasberg, indicates that the biology is favorable for the use of this tracer to assess DNA synthetic rate, particularly in brain tumors. Serious questions remain, however, about whether enough IUdR will be taken up to permit statistically accurate quantitative imaging, either with SPECT (I-131, I-123) or PET (I-124) . We will do limited patient demonstration studies to assess this.

B. PLANNED CONTINUATION OF RESEARCH OBJECTIVES : We are seeking a practical method of study of MDR *in vivo*, using radiotracer techniques. We want to use these methods to improve our understanding of the biology of acquired or intrinsic resistance based on the MDR phenotype. We will continue with parallel studies using MRK-16 to probe the concentration of pGP and colchicine to assess the functional capacity for excluding drugs of the MDR phenotype. We will evaluate the ability of C-11 colchicine to document strategies that promote resistance *in vitro* and *in vivo*. We plan FAX and autoradiographic studies to correlate the expression of pGP at the individual cell level, with the overall resistance or sensitivity of the tumor cells *in vitro* and *in vivo*. Recent use of alpha interferon suggests enhancement of the MDR phenotype, and we will study this phenomenon in our system to determine the role that pGP expression may play in this enhanced resistance, and whether or not there is an interaction with other agents such as verapamil, which are known to increase resistance but on a functional basis. We will also study the role of MRK-16 itself in the reversal of the MDR phenotype. Since this system is well characterized, we will also study other possible markers of the MDR phenotype, such as Tc-99m sestimibi. *In vitro* systems, we will compare this agent with C-14 colchicine, or H-3 colchicine, and we will explore the stoichiometry of this agent in regard to the actual molar quantitative expression of pGP, as measured with our binding assays. Eventually, if radiochemistry program to make Tc94m sestimibi is successful, we will evaluate the potential of this agent for positron imaging, initially using *in vitro* methods, and QAR methods. For clinical purposes, the longer half-life of the Tc positron emitters, may be an advantage for pharmacokinetic purposes. PET imaging will permit quantitation to be significantly better than SPECT techniques.

Studies of IUdR will be pursued with I-124 IUdR, to followup on the interesting observation of the peripheral localization of proliferating brain tumor cells in patients with gliomas and CNS lymphomas. In addition, the IUdR will be used in studies of the dosimetry of IUdR for therapy (See 2B below).

Since Dr. Bertino has expressed renewed interest in labeled methotrexate studies, we plan to pursue the use of Iodomethotrexate, if it can be conveniently labeled by the radiochemistry group. Studies will be performed to correlate the retention of Iodomethotrexate with tumor resistance to various methotrexate analogues.

Project 3. Immunology

Project 3A Quantitative immunokinetics and dosimetry of anti-tumor antibodies

A. Original Objectives: To thoroughly evaluate the imaging physics of detection and quantification of I-124 and Ga-66 like radionuclides with modern PET scanners. and 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. Quantitative imaging approaches with PET will be used in order to validate standard imaging approaches obtained through SPECT.

B. Planned Continuation of Objectives: The delay in installing the GE ADVANCE SCANNER, caused us to change directions in the preceding grant period, toward dosimetry methods based on SPECT and planar imaging. As described above, this program was successful, in that several novel approaches were developed that have led to the beginnings of an improved understanding of radiation absorbed doses delivered by internal emitters, such as radiolabeled antibodies, I-131 ion for treatment of thyroid cancer, and Auger emitting radionuclides labeled to Iododeoxyuridine. In the next grant period under the current DOE grant , we plan to focus on **non-antibody** dosimetry, in particular, nucleosides such as Iododeoxyuridine labeled with I-123 and I-131. Based on our initial pilot studies, we will extend our evaluation of the feasibility of IUdR therapy of human colorectal metastases. The patient population is available for study because of an ongoing grant which studies various treatment modalities for metastatic colorectal cancer to liver. Dr. Nancy Kemeny, a collaborator of ours, has had extensive experience with interhepatic therapies and in collaboration with her group, we have performed preliminary experiments in 4 patients. The approach shows promise, and toxicity was not present in preliminary studies. We intend to validate our current quantitation techniques using PET scanning and I-124 IUdR. We intend to study the kinetics of localization and clearance of IUdR in human tumors and other normal tissues (such as bone marrow and gut), and based on this we will develop compartmental models which can be used in treatment planning. In particularly, we are concerned with the reproducibility of uptake, methods to enhance uptake, and estimation of the fraction of activity incorporated into DNA, non-invasively, using these models. Also, we will extend our current assessment of tumor control probability for cycle specific agents such as IUdR, based on the results of the patient studies. We will compare various labels which may be most effective, particularly I-123, I-124 versus I-125. We have recently added considerable expertise in the area of local deposition of energy in the nuclear region with Dr. John Humm's appointment to our physics group and Dr.s Daghighian, Sgouros and Humm will combine efforts in theoretical considerations, experimental design, and data analysis. We will also take advantage of the opportunity afforded us by the large number of patient with thyroid cancer, to begin to develop more quantitative information about the relationship between radiation dose and thyroid cancer tumor response at various sites in the body. PET imaging of I-124 iodide will be performed in selected patients with tumors whose tumor volume is readily measurable on cross-sectional imaging.

PET may be a break-through technology for the detection of certain human tumors. Certainly FDG PET imaging of colorectal Ca., Breast Cancer, Melanoma, Lung cancer, shows outstanding promise for improved detection and staging of human cancers. The limits of tumor detection with PET, and the dependence on tumor/background ratio, as well as tumor concentration of radioactivity on the imaging physics of detection of small tumors has not been well studied. We will study the impact on tumor detectability of various imaging parameters, such as reconstruction, attenuation correction "3-D" imaging without septa; scatter correction ; total dosage of radiopharmaceutical used; image time duration; count statistic issues; the value of "Whole-Body(rectilinear) mode." These studies will be done in order to optimize tumor detection. We will employ ROC analysis and anthropomorphic phantoms designed to simulate realistic clinical conditions. We plan to take advantage of clinical studies that involve surgical biopsy to validate

scan findings wherever possible. These studies, if successful, are likely to have a major impact in determining when PET is going to be effective for tumor image, and will provide a basis for systematic application to diagnostic situations.

Project 3B. Artificial Lymphatic System.

A. Original Objectives: The aim of this study was to evaluate the efficacy of an artificial lymphatic system(ALS) to reduce interstitial hypertension and enhance uptake of therapeutic agents. Three objectives were pursued: 1) Development of methodology to measure pertinent transport parameters 2) Characterization of IFP, IFV, pH, pO_2 and rGMR in the human neuroblastoma rat xenograft model and 3) Measure specific and non-specific monoclonal antibody(moab) uptake before and after IFP manipulation.

B. Planned Continuation and New Objectives

Our findings suggest that it is the reduced tumor blood flow and the adverse effects it has on tumor tissue milieu, i.e. acidic pH, which contributes to the ineffectiveness of antibody - antigen reaction kinetics. Simply put the moab may arrive at an antigenic site, but will not bind. Our findings have shown that reducing IFP with an ALS will increase tumor blood flow. We anticipate that this effect will restore the milieu to a more kinetically favorable environment and make those moabs which arrive more effective. In addition our pO_2 studies will determine if tumor oxygen levels can be elevated and thus make the tumor more radiation sensitive.

We are now planning to :

1. Repeat the uptake studies using our fully implantable multi-probe ALS system to determine the maximum drug uptake which can be expected when IFP is uniformly reduced throughout a tumor.

2. Consider the efficacy of ALS treatment during administration of chemotherapy or radiotherapy. This work will determine if the additional drug will "kill" tumors or make them more radiosensitive. Tumor kill effectiveness will be determined using tumor shrinkage and PET FDG studies.

3. Develop a non-invasive scheme to measure hydrodynamic impedance using PET and an F-18 macromolecule.

4. Develop a mathematical probe placement scheme which will be used to optimally place ALS probes within tumors of any geometry. We will adapt concepts from brachytherapy for our analytical paradigm. Our data sets will include CT/MRI and PET images.

These studies will contribute to the development of the tools and generate the efficacy data necessary before human clinical trials can be started.

3.0 GRADUATE STUDENTS TRAINED:

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.

4. Rosa E. (Masters). Identification of multidrug resistance tumors. (May 1993), Manhattan College and College of Mt. St. Vincent Biotechnology (1993).

5. Yoshinuri Futimoto (Masters) :Quantitation of In - vivo radioactivity with CT aided attenuation correction and subtraction of normal tissue radioactivity in conjugate view method. Hunter College Physics (1995)

6. Andrey Levchenko (Masters) : Monovalent Ligand-receptor interaction: analysis of theoretical approximations. Columbia University , Bioengineering (1995)

Trainees:
Under the direction of Dr. Finn

1. Vipa Boonkitticharoen, Ph.D. International Atomic Energy Agency Fellow. Tc-99m labeling of 3F8 monoclonal antibody.

2. S. Cai, Ph.D(Post-Doctoral studies): Synthesis of fluorine-18 radiolabeled HM-195.

3. T.K. Nikula,M.S.(Turkuu Finland). Chelation chemistry of radiometals for antibody labeling.

Under the Direction of Dr.s Larson and Mehta:
4. Diu-Thu Vo, M.D. (Post-doctoral fellow) Factors important to the localization of radiolabeled 3F8 to human tumors.

5. Rosa Fonti, M.D. (University of Naples): Quantitative Autoradiographic studies of p-glycoprotein expression in normal and malignant human tissues.

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

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5. Yoshinuri Futimoto (Masters) :Quantitation of In - vivo radioactivity with CT aided attenuation correction and subtraction of normal tissue radioactivity in conjugate view method. Hunter College Physics (1995)

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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.

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16. Graham MC, et al. Evaluation of Ga-66 as an isotope for tumor detection and quantitative monoclonal dosimetry using PET. American Assoc of Physicists in Medicine (AAPM) Aug 8-12, 1993.

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18. Scott AM, Rosa E, Carmichael N, Finn RD, Divgi CR, Biedler JL, Tsuruo T, Mehta BM, Larson SM. In vivo quantitation of p-glyco-protein receptor expression with I-125 MRK-16 mAb. Proceedings - 84th Annual Meeting Amer Assoc for Can Research 1993, 34:1866.

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23. Scott AM, Sgouros G, Divgi CR, Zhang JJ, Pentlow K, Daghighian H, Schlom J, Wheatley J, Macapinlac H, Graham MC, Kalaigian H, Schlom J, Larson SM. Clinical implementation of combined 3-D and MIRD-based dosimetry for radioimmunotherapy with I-131 CC49 monoclonal antibody (MAB). J Nuc Med, Proceedings 40th Annual Meeting 1993, 34;5:127P.

24. Sgouros G, Chiu S, Pentlow KS, Brewster LJ, Kalaigian H, Baldwin B, Daghighian F, Graham MC, Larson SM, Mohan R. Three-dimensional dosimetry for radioimmunotherapy treatment planning. J Nuc Med, Proceedings 40th Annual Meeting 1993, 34;5:162P.

25. Scott AM, Baselga J, Divgi CR, Pfister D, Kris M, Zhang JJ, Daghighian F, Carmichael N, Oettgen HF, Larson SM, Mendelsohn J. Comparison of phase I trials of anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (Mabs) 528 and 225 labelled with I-131 and In-111. J Nuc Med, Proceedings 40th Annual Meeting 1993, 34;5:213P.

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28. Kairemo KJA, Sgouros G, Levchenko A, Kostakoglu L, Fisher DR, Scott AM, Daghighian F, Divgi CR, Mehta BM, Rosa E, Finn RD, DiResta GR, et al. Kinetics and tumor targeting by using a single-chair FV derived from the TAG72 monoclonal antibody CC49: Considerations for labeling with positron emitters and effects of interstitial fluid pressure on tumor uptakes. Europ Assoc Nucl Med Congress, Oct. 1993.

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31. Arbit E, DiResta GR, Lee J, Volkert-Faizinger R, Bral P. The effect of nimodipine on cerebral elastance and edema in a cryogenic injury model. 9th Internation Symposium on Intracranial Pressure: ICP and its related problems; Nagoya, Japan; May 16-19, 1994.

32. Arbit E, Lee J, DiResta GR. Direct correlation between interstitial fluid pressure and brain edema found in human brain tumors in situ. 9th International Symposium on IntraCranial Pressure:ICP and its related problems; Nagoya, Japan; May 16-19th, 1994.

33. Mehta BM, Rosa E, Kim SW, Scott AM, Zhang J, Kalaigian H, Sgouros G, Divgi CR, Larson SM. Evaluation of ^{14}C-colchicine biodistribution in colchicine -sensitive and -resistant xenografts using 3D fusion imaging. Proceedings of American Association for Cancer Research 1994; #2018.

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35. Kostakoglu L, Finn R, DiResta G, Pentlow K, Lee J, Mawlawi O, Larson SM. Ga-66 Citrate: A novel tumor localization agent for PET. Proceedings of AACR, March 1994; 35: p527.

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38. Mehta BM, Levchenko A, Broussard E, Kothari PH, Patel DA, Finn RD, Larson SM. ^{11}C-Colchicine Distribution in Tissues of Colchicine -sensitive and -resistant Neuroblastoma Xenografts. J. Nucl. Med. 1995; 36:189P.

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Patents

1. 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)

2. Continuation In Part to ALS; submitted March 1995; {Additional components of ALS device and process}.

5.0 FEDERAL SUPPORT

CURRENT AND PENDING SUPPORT

Steven M. Larson, M.D.

(1) Currently active support:

(a). Department of Energy, DE-FG02-86ER60407
Improving Cancer Treatment with Cyclotron Produced Radionuclides
Steven M. Larson, M.D., P.I.; R.D. Finn, Ph.D., Co-P.I.
Percent of Appointment: 25% effort only
Dates of Entire Project: 2/1/93-1/31/96
Annual Direct Costs: $290,694

(b). National Cancer Institute NCDDG 001-CA37641
Antireceptor Monoclonal Antibody in Cancer Treatment
John Mendelsohn, M.D., Principal Investigator
Percent of Appointment: 5% effort only
Dates of Entire Project Period: 8/1/90 to 7/31/95
Annual Direct Costs: $775,864

(c). National Cancer Institute #U01 CA 58260
Radioimmunotherapy Dosimetry Modeling in CML
David Scheinberg, M.D., Principal Investigator
Percent of Appointment: 5%
Dates of Entire Project Period: 9/30/92-9/29/96
Annual Direct Costs: $156,957

(d). National Cancer Institute #PO1 CA 52477
Epithelial Ovarian Cancer Program Project
William J. Hoskins, M.D., Principal Investigator
Percent of Appointment: 15%
Dates of Entire Project Period: 4/1/91-3/31/98
Annual Direct Costs: $630,914

(e) National Cancer Institute #CA47179-04A1
Soft Tissue Sarcoma Program Project
M. Brennan, M.D., Principal Investigator
Percent of Appointment: 5% effort only
Dates of Entire Project Period: 7/1/92-6/30/95
Annual Direct Costs: $572,000

(f) Department of Energy #DE FG-0293ER61658
Single chain Fv constructs of anti-ganglioside GD2 antibodies for radioimaging and radioimmunotherapy
N. V. Cheung, M.D., P.I.; S.M. Larson, M.D., Co-P.I.
Percent of Appointment: 4%
Dates of Entire Project: 8/1/93-1/31/97
Annual Direct Costs: $205,308

(g). National Cancer Institute 1 RO1 CA55531-01
Monoclonal Antibody Treatment of AIDS-Related Lymphoma
David J. Straus, M.D., Principal Investigator

Dates of Entire Project Period: 7/1/91-6/30/96
Percent of Appointment: 5% effort
Annual Direct Costs: $145,326

(h). National Cancer Institute, CORE, #2 POl CA 33049-12
Monoclonal Antibodies & Vaccines in Cancer Therapy (Nuclear Medicine Core)
A. Houghton, M.D., Principal Investigator
Percent of Appointment: 5% effort only
Dates of Entire Project Period: 12/1/94-11/30/99
Annual Direct Costs: $152,035

(i). Department of Energy DEF602-95-ER62039
Pharmacokinetics of Genetically Engineered Antibody Forms Using Positron Emission Tomography
S.M. Larson, M.D., Principal Investigator
Percent of Appointment: 10%
Dates of Entire Project Period: 05/01/95-02/28/98
Annual Direct Costs: $399,811

Ronald D. Finn, Ph.D.

(1) Currently Active Support:

(a). Department of Energy, DE-FG02-86ER60407
Improving Cancer Treatment with Cyclotron Produced Radionuclides
Steven M. Larson, M.D., P.I.; R.D. Finn, Ph.D., Co-P.I.
Percent of Appointment: 33%
Dates of Entire Project: 2/1/93-1/31/96
Annual Direct Costs: $290,694

(b). Department of Energy #DE FG-0293ER61658
Single chain Fv constructs of anti-ganglioside GD2 antibodies for radioimaging and radioimmunotherapy
N. V. Cheung, M.D., P.I.; S.M. Larson, M.D., Co-P.I.
Percent of Appointment: 7%
Dates of Entire Project: 8/1/93-1/31/97
Annual Direct Costs: $205,308

(c). Food and Drug Administration FD-R-001041-01
MOAB Targeted Radiotherapy to Ablate Neuroblastoma
BBIND 2299
N.V. Cheung, M.D., P.I.
Percent of Appointment: 5%
Dates of Entire Project: 07/01/94-06/30/97
Annual Direct Costs: $98,656

(d). National Cancer Institute #U01 CA 58260
Radioimmunotherapy Dosimetry Modeling in CML
David Scheinberg, M.D., Principal Investigator

Percent of Appointment: 5%
Dates of Entire Project Period: 9/30/92-9/29/96
Annual Direct Costs: $156,957

(e). National Institutes of Health CA-08748
Cancer Center Support Grant
P.A. Marks, M.D., Principal Investigator
Percent of Appointment: 33%
Dates of Entire Project: 01/01/93-12/31/97
Annual Direct Costs: N/A

(f). National Cancer Institute, CORE, #2 POl CA33049-12A1
Monoclonal Antibodies & Vaccines in Cancer Therapy (Nuclear Medicine Core)
A. Houghton, M.D., Principal Investigator
Percent of Appointment: 10%
Dates of Entire Project Period: 12/1/94-11/30/99
Annual Direct Costs: $152,035

(g). National Institutes of Health 2R01-MH 40671-06AZ
PET Studies of Attention in Schizophrenia
Monte Buchsbaum, M.D., P.I.
Percent of Appointment: 10%
Dates of Entire Project Period: 09/30/92-8/31/95
Annual Direct Costs: $48,000

(h). National Institutes of Health RO1-CA55349-01
Recombinant Anti CD-33 Antibody
D.A. Scheinberg, M.D., P.I.
Percent of Appointment: 5%
Dates of Entire Project Period: 09/01/94-08/30/98
Annual Direct Costs: $8,000

(2) Pending:

(a). National Institutes of Health - RO1
Imaging Gene Transfer and Expression
R.G. Blasberg, M.D., P.I.
Percent of Appointment: 10%
Dates of Entire Project Period: 12/01/95-11/30/98
Annual Direct Costs: $1 million (total costs requested)

(b). National Center for Research Resources RR-95-003
The Expanded Cyclotron Program at MSKCC
R.D. Finn, Ph.D., P.I.
Dates of Entire Project Period: 1996
Annual Direct Costs: $1,491,000 (Institutional Matching Amount) Total Costs