

Progress Report

Cyclotron Produced Radionuclides for Diagnosis and Therapy of Human Neoplasms

DE86ER60407

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Grant objectives

Project 1: DE86ER60407 This project funded since 1986 serves as a core project for cancer research throughout MSKCC, producing key radiotracers as well as basic knowledge about the physics of radiation decay and imaging, for nuclear medicine applications to cancer diagnosis and therapy. In recent years this research application has broadened to include experiments intended to lead to an improved understanding of cancer biology and into the discovery and testing of new cancer drugs.

Project 2: 95ER62039. Advances in immune based radiotargeting form the basis for this project. Both antibody and cellular based immune targeting methods have been explored. The multi-step targeting methodologies (MST) developed by NeoRex (Seattle, Washington), have been adapted for use with positron emitting isotopes and PET allowing the quantification and optimization of targeted delivery. In addition, novel methods for radiolabeling immune T-cells with PET tracers have advanced our ability to track these cells of prolonged period of time.

Major Accomplishments

Project 1

- 1. *Radioisotope and radiotracer development.*** Significant developments have been made in cyclotron targetry to allow the production of practical levels of long lived PET isotopes including iodine-124 and yttrium-86. These isotopes are now established as important PET isotopes for applications in targeted therapy and other applications involving agents with slow tumor uptake times, and are now being used in clinical trials at MSK.
- 2. *Radiotracers for Cancer Diagnosis and Therapy*** This funded project has contributed to the development of more than forty radiotracers, many of which have served as the basis for biologic discovery. Of these, 20 formulations are completely novel, and range from small molecules, such as substrates, drugs and hypoxia tracers, to large proteins, such as monoclonal antibodies against human tumors. Recent radiotracers have included molecules to assess signal transduction, tyrosine kinase inhibitors for EGFR and abl kinases, agents that target HSP90 etc. One the key developments of this grant has been the development of different radiolabeled forms of the un-natural nucleoside, fluoridoarabinosyluridine (FIAU). This synthetic nucleoside FIAU has been the basis for nuclear imaging of gene expression, a foundation stone in the science of molecular imaging.

- 3. Radionuclide generator systems** One key advancement resulting from this DOE project has been the development of an actinium-225 generator, allowing the production of the short-lived isotope bismuth-213 for alpha targeted radioimmunotherapy. This work resulted in the first clinical radioimmunotherapy trial using an alpha emitter in the World being performed at MSKCC with the ²¹³Bi-M195 antibody in patients with leukemia. This was made possible through DOE funded column development.
- 4. Medical Physics Advances** which support biologic initiatives have been in several areas including: imaging corrections methods for positron emitters, which release complex prompt photon spectra, e.g. iodine-124 and yttrium-86 that cannot be eliminated by timing or energy discrimination, patient specific radionuclide dosimetry using novel radionuclide therapy treatment planning systems, quantitative digital autoradiography, small animal stereotactic image registration techniques and most recently hypoxia imaging using a novel ¹²⁴I tracer iodoazomycin galactosidase(¹²⁴I-IAZGP), which has led to the funding of a new NCI program project grant with a focus on non-invasive imaging of tumor hypoxia.

Project 2: Novel Approaches to Targeted Radioimmunotherapy 95ER62039.

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- 1. Development of 5F11 sfv/avidin fusion, a novel anti-GD2 tetrameric antibody** has been accomplished through this collaboration and shown to target to GD2 expressing animal models. GD2 is an important antigen target that is expressed on pediatric brain tumor such as neuro- and medullo-blastoma, small cell lung carcinoma and melanoma. These studies dovetail with ongoing successful clinical radioimmunotherapy trials using the ¹³¹I-labeled 3F8i and provide important pre-clinical information on methods to advance ongoing clinical pediatric therapy trials.
- 2. Successful PET imaging of Yttrium-86, Gallium-66, and Gallium-68** Several pre-clinical studies have been performed under this DOE funding demonstrating for the first time the feasibility of quantitative PET imaging to determine tumor uptake and for radionuclide dosimetry.
- 3. Gene directed labeling of T-cells using FIAU** The first work to use the reporter gene technology to successfully track human EBV lymphoma tumor injected into mice arose from this funded grant. This work allows for an improved specificity of tracking T-cells via a gene directed and selective uptake of the FIAU reporter probe. This advance will facilitate improved in vivo monitoring of adoptive immunotherapy, in which immune cells are prepared outside the body, and then administered to a patient for the purposes of therapy against a human tumor.

The objective accomplishments resulting from DOE funding at MSKCC is best summarized by the achievements in terms of the number of publications, NIH funded grants that utilize radiotracers

developed under DOE funding and a list of those tracers themselves. These are given on the 3 sections below.

References originating from DOE support since 2000

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List of Grants Arising from Radionuclides Provided by DOE Support

<i>PI Name</i>	<i>Number</i>	<i>Agency</i>	<i>Title</i>	<i>DOE Tracer or Contribution</i>
Blasberg R.	CA57599	NCI	IUDR Imaging of Tumor Proliferation	¹²⁴ IUDR
Blasberg R	CA60706	NCI	Brain Tumor Imaging with Non-Metabolized Amino Acids	¹⁸ F amino-acids;
Blasberg R	CA69769	NCI	Imaging Gene Transfer and Expression	¹²⁴ I-FAIU
Fong Y	CA72632	NCI	Acceleration of Tumor Growth by Liver Resection	¹²⁴ IUDR
Fong Y	CA75416	NCI	Liver Regeneration in Man: Effects of Adjuvant Therapy	¹²⁴ IUDR
Divgi C	CA78642	NCI	Intraperitoneal Radioimmunotherapy in Ovarian Cancer	⁸⁶ Y
Ling CC	P01 CA115675	NCI	Tumor Hypoxia Imaging	¹²⁴ I-IAZGP, hypoxia tracers
Sgouros G	CA62444	NCI	Modeling and Dosimetry for Radiolabeled Antibody Therapy	Dosimetry model develop.
Sgouros G	CA72683	NCI	Antibody Therapy of Micrometastases	Dosimetry Models/ ²¹³ Bi
Tjuvajev J	CA76117	NCI	Imaging Multi-Gene Transductions	¹²⁴ I- ¹⁸ F FAIU and analogs
Tjuvajev J	CA80054	NCI	Imaging E.Coli XGPRT Marker Gene Transfer and Expression	¹²⁴ I- ¹⁸ F-FAIU and analogs

Radionuclides developed at MSKCC under DOE support

Radionuclide	Compound	Comments
C-11*	Colchicine –C11	MDR studies
C-11	n-methyl AIB- C11	Unnatural amino acid
C-11	Methionine	Prostate Ca studies
I-124*	Iododeoxyuridine (IUDR)	Proliferation agent
I-124*	FIAU, FIRU and 3 analogs	Gene imaging agents
I-124 *	3f8,M195,CC49	Tumor targeting antibodies
I-124*	Iodomethotrexate	Pharmacology studies
I-124	Sodium Iodide	Thyroid cancer dosimetry
I-124	Iodo-Azomycin-Galactoside (IAZG)	Hypoxia
F-18*	Ascorbate	Transport studies
F-18*	M195	Fluorinated antibody
Ga-66*	Citrate	PET gallium
Y-86*	M195, CC49	Targeted antibody program
Y-88	Chloride	Long lived Y tracer
Ac-225/Bi-213 *	Generator system	Useable generator system Tumor targeting antibodies

*Novel synthesis or formulation