Office of Science
Notice DE-FG01-04ER04-17

Innovative Technologies for In Vivo Targeted Radiopharmaceutical Dose Delivery and Deposition

Department of Energy

Office of Science Financial Assistance Program Notice DE-FG01-04ER04-17; Innovative Technologies for *In Vivo* Targeted Radiopharmaceutical Dose Delivery and Deposition

AGENCY: U.S. Department of Energy

ACTION: Notice inviting grant applications.

SUMMARY: The Office of Biological and Environmental Research (OBER) of the Office of Science (SC), U.S. Department of Energy (DOE), hereby announce its interest in receiving grant applications to support one specific research area within the Medical Applications Program: Innovative Technologies for ***In Vivo*** Targeted Radiopharmaceutical Dose Delivery and Deposition. The emphasis will be on the therapeutic use of ionizing radiation. The specific goals include: 1) development of radiochemical methodologies for labeling the targeting molecules with and for site-specific delivery of therapeutic dose levels of radioactivity, and 2) development of radiobiology-based-microdosimetry techniques to accurately measure and predict the potential therapeutic use, dose and dose rate delivery of ionizing radiation. Applicants are encouraged to propose innovative methodologies and technologies to label biological ligands with therapeutic level radioactivity, ensure ***in vivo*** delivery of intact radioisotopically labeled molecules to specific tumor cell types, and develop novel microdosimetry paradigms. Applications for clinical trials using already developed compounds and techniques will not be considered.

DATES: Before preparing a formal application, potential applicants are encouraged to submit a brief preapplication. All preapplications referencing Program Notice DE-FG01-04ER04-17, should be received by DOE by 4:30 p.m., Eastern Time, April 12, 2004. A response encouraging or discouraging the submission of a formal application will be communicated by electronic mail within approximately 2 weeks.

Formal applications submitted in response to this Notice must be received by 4:30 p.m., Eastern Time, June 15, 2004, to be accepted for merit review and be considered for award in Fiscal Year 2004 or early 2005.

ADDRESSES: Preapplications referencing Program Notice DE-FG01-04ER04-17, are to be sent, if possible, by E-mail or Fax to Ms. Sharon Betson (sharon.betson@science.doe.gov; Fax: 301-903-0567). Preapplications will also be accepted if mailed to the following address: Ms.

Sharon Betson, Office of Biological and Environmental Research, SC-73, 19901 Germantown Road, Germantown, MD 20874-1290.

Formal applications referencing Program Notice DE-FG01-04ER04-17, must be sent electronically by an authorized institutional business official through DOE's Industry Interactive Procurement System (IIPS) at: http://e-center.doe.gov/. IIPS provides for the posting of solicitations and receipt of applications in a paperless environment via the Internet. In order to submit applications through IIPS, your business official will need to register at the IIPS website. **IIPS offers the option of using multiple files, please limit submissions to one volume and one file if possible, with a maximum of no more than four PDF files.** The Office of Science will include attachments as part of this notice that provide the appropriate forms in PDF fillable format that are to be submitted through IIPS. Color images should be submitted in IIPS as a separate file in PDF format and identified as such. These images should be kept to a minimum due to the limitations of reproducing them. They should be numbered and referred to in the body of the technical scientific grant application as Color image 1, Color image 2, etc. Questions regarding the operation of IIPS may be E-mailed to the IIPS Help Desk at: HelpDesk@pr.doe.gov, or you may call the help desk at: (800) 683-0751. Further information on the use of IIPS by the Office of Science is available at: http://www.sc.doe.gov/production/grants/grants.html.

If you are unable to submit an application through IIPS, please contact the Grants and Contracts Division, Office of Science at: (301) 903-5212 or (301) 903-3604, in order to gain assistance for submission through IIPS or to receive special approval and instructions on how to submit printed applications.

FOR FURTHER INFORMATION CONTACT: Prem C. Srivastava, Ph.D., Office of Biological and Environmental Research, Medical Sciences Division, SC-73, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290, telephone: (301) 903-4071, FAX: (301) 903-0567, E-mail: prem.srivastava@science.doe.gov. The full text of Program Notice DE-FG01-04ER04-17 is available via the Internet using the following web site address: http://www.sc.doe.gov/production/grants/grants.html.

SUPPLEMENTARY INFORMATION: The BER Medical Applications Program supports directed nuclear medicine technology research in the areas of radiopharmaceutical development, molecular nuclear medicine and advanced biomedical imaging to promote the use of radioisotopes for non-invasive diagnosis and therapy.

The early BER programs focused on understanding the physical, chemical and biologic consequences of radionuclide decay in the human body. Those studies led to much of the basic information that is still used today to describe the therapeutic effects of targeted radionuclides. DOE continued to fund projects and develop technologies for therapeutic effect and use of radiation that generated much of the current knowledge in radioisotope chemistry, identification of targeting agents, methods for chemical coupling of isotopes to targeting agents, scanning and imaging techniques, mathematical modeling and internal radiation dosimetry. This research has formed the basis for many current cancer targeted radionuclide therapy modalities in various stages of development.

Current themes have developed about radiation's main molecular targets, absorbed energy doses and resultant radiation damage. This has led to the development of defined absorbed doses (Gy, Sv) that dominate our predictions about tumor destruction and normal tissue damage. Most radiobiology has been focused on radiation damage induced by high dose rate gamma and neutron exposures. Targeting with electrons, alpha and beta emitters employed at intermediate to low dose rate intensities requires a much better understanding of radiation damage to cells, and new paradigms need to be addressed to understand how best to use radioisotopes for selective destruction of solid tumors as compared to normal tissue. The recent emphasis on targeted radiopharmaceutical therapy agents against many forms of cancer has brought about an increase in the need for reliable and clinically meaningful, patient-specific internal dose calculations. The ability to link radiation dose to observed biological effect of radiation is complicated by a number of factors, including the heterogeneity of the activity distribution within normal organ tissue or within tumors, the range of the particles delivering the therapeutic dose, the total dose received, the dose rate at which the dose is delivered, (which depends on the radionuclide half-life), and the radiosensitivity of the tumor cells.

Basic research in molecular biology has provided new insights to the molecular basis of human disease and its potential molecular targets. DOE's current Molecular Nuclear Medicine Program encourages development of new technologies for molecular delivery of radioisotopes to disease target sites with a high degree of precision, recognition, and target selectivity. The availability of new technology for high resolution imaging of small animals should facilitate the evaluation of the biological effects of ionizing radiation.

This Notice is to solicit grant applications for developing innovative technologies for ***in vivo*** targeted radiopharmaceutical dose delivery and improved radiotoxic dose deposition in the target as compared to normal tissue. A well integrated team effort by scientists from overlapping disciplines of radiochemistry, radiopharmaceutical chemistry, cellular and molecular radiobiology, radiation oncology, targeted radiation therapy, microdosimetry and modeling will be important. Methodological approaches and sensitive technologies that can be adapted to deliver, deposit, measure and predict therapeutic levels of radiation dose to the target sites are sought. It will be important for each application to address also the following objectives:

1. Radiolabeling of targeting molecules at therapeutic dose levels of radioactivity.

2. Considerations of radiochemical and *in vivo* biological viability (activity, stability, target specificity, and selectivity) of the molecule, against sensitivity to structural perturbations in the molecule as a result of radiolabeling.

3. Radiopharmaceutical delivery of intact radioisotopically labeled molecules to tumor cells in therapeutic dose amounts.

4. Innovative measurement techniques for evaluating biological effects of therapeutic radiation at low dose rates in vivo at the molecular, cellular and metabolic levels.

5. Modeling and microdosimetry methods for understanding the biological effects of radiation at the cellular and subcellular level for guiding predictions about optimum radiation dose, radiation dose rate, and resultant tumor destruction and normal tissue damage.

6. Measurement techniques for accurately assessing the success of tumor targeting in vivo.

7. The research plan will support BER Medical Applications long term performance goals in scientific advancement by providing innovative radiopharmaceutical methodologies or technologies for use in solid tumor cell destruction. Applicants should note that only a methodology or a technology offering promise for intended use, and not the experimental data resulting from the proposed research will be considered an accomplishment and will contribute to the measures of performance.

Program Funding

It is anticipated that up to $2 million will be available for multiple awards starting Fiscal Year 2004 to Fiscal Year 2005, contingent upon the availability of appropriated funds and the scientific merit of the submitted applications. Previous awards have ranged from $200,000 to $400,000 per year (direct plus indirect costs) with terms lasting up to three years. Award sizes of approximately $400,000-$500,000 are anticipated for new, well integrated, multidisciplinary research grants. Applications may request project support up to three years, with out-year support contingent on the availability of appropriated funds, satisfactory progress in the research proposed, and programmatic needs.

Preapplications

A brief preapplication should be submitted. The cover sheet of the preapplication should list the title of the project, the institution, and the principal investigator's name, address, telephone, fax, and E-mail address. The preapplication should not exceed two pages (in addition to the cover sheet). It should identify and describe the research objectives, the methods proposed for accomplishment of the research, and the key members of the scientific team responsible for this effort. Preapplications will be evaluated relative to the scope and objectives of this solicitation.

Merit Review

Applications will be subjected to scientific merit review (peer review) and will be evaluated against the following evaluation criteria listed in descending order of importance as codified at 10 CFR 605.10(d):

1. Scientific and/or Technical Merit of the Project
2. Appropriateness of the Proposed Approach and Methods
3. Competency of the Research Team and Adequacy of Available Resources
4. Justification of the Proposed Budget.

The evaluation will include program policy factors such as the relevance of the proposed research to the terms of the announcement and the agency's programmatic needs. It should be

noted that external peer reviewers are selected on the basis of their scientific expertise and the absence of conflict-of-interest issues. Non-federal reviewers may be used, and submission of an application constitutes agreement that this review process is acceptable to the investigator(s) and the submitting institution.

Submission Information

Information about the development, submission of applications, eligibility, limitations, evaluation, the selection process, and other policies and procedures may be found in 10 CFR Part 605, and in the Application Guide for the Office of Science Financial Assistance Program. Electronic access to the Guide and required forms is made available via the World Wide Web at: http://www.sc.doe.gov/production/grants/grants.html. DOE is under no obligation to pay for any costs associated with the preparation or submission of applications if an award is not made. In addition, in response to this Notice, the Project Description must be 25 pages or less, exclusive of attachments, and the application must contain a table of contents, an abstract or project summary, letters of intent from collaborators (if any), and short curriculum vitae, consistent with National Institutes of Health guidelines. Block 15 of the SC grant face page (form DOE F4650.2) should list the PI's phone number, fax number, and E-mail address.

DOE policy requires that potential applicants adhere to 10 CFR 745 “Protection of Human Subjects” or such later revision of those guidelines as may be published in the Federal Register. The Office of Science as part of its grant regulations requires at 10 CFR 605.11(b) that a recipient receiving a grant and performing research involving recombinant DNA molecules and/or organisms and viruses containing recombinant DNA molecules shall comply with NIH "Guidelines for Research Involving Recombinant DNA Molecules," which is available via the world wide web at: http://www.niehs.nih.gov/odhsb/biosafe/nih/rdna-apr98.pdf, (59 FR 34496, July 5, 1994,) or such later revision of those guidelines as may be published in the Federal Register.

The Catalog of Federal Domestic Assistance number for this program is 81.049, and the solicitation control number is ERFAP 10 CFR Part 605.

Martin Rubinstein
Acting Director
Grants and Contracts Division
Office of Science

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