Program Announcement
To DOE National Laboratories
LAB 04-17

Innovative Technologies for In Vivo Targeted Radiopharmaceutical Dose Delivery and Deposition

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 proposals 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. Researchers 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. Proposals for clinical trials using already developed compounds and techniques will not be considered.

DATES: Before preparing a formal proposal, potential researchers are encouraged to submit a brief preproposal. All preproposals referencing Program Announcement LAB 04-17, 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 proposal will be communicated by electronic mail within approximately 2 weeks.

Formal proposals submitted in response to this Announcement 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: Preproposals referencing Program Announcement LAB 04-17, are to be sent, if possible, by E-mail or Fax to Ms. Sharon Betson (sharon.betson@science.doe.gov; Fax: 301-903-0567). Preproposals 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 proposals in response to Program Announcement LAB 04-17 are to be submitted as 2 paper copies of the proposal and one CD containing the proposal in PDF format. Color images should be submitted 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 hardcopies. They should be

numbered and referred to in the body of the technical scientific proposal as Color image 1, Color image 2, etc.

The 2 copies of the proposal and the CD, referencing Program Announcement LAB 04-17, should be sent to: Ms. Sharon Betson, Office of Biological and Environmental Research, SC-73, 19901 Germantown Road, Germantown, MD 20874-1290, ATTN: Program Announcement LAB 04-17.

When submitting by U.S. Postal Service Express Mail, any commercial mail delivery service, or when hand carried by the researcher, the following address must be used: Ms. Sharon Betson, Office of Biological and Environmental Research, SC-73, Office of Science, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290, ATTN: Program Announcement LAB 04-17.

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.

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 Announcement is to solicit proposals 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 proposal 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 proposals. 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 awards. Proposals 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. DOE is under no obligation to pay for any costs associated with the preparation or submission of proposals if an award is not made.

Preproposals

A brief preproposal should be submitted. The cover sheet of the preproposal should list the title of the project, the institution, and the principal investigator's name, address, telephone, fax, and E-mail address. The preproposal 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. Preproposals will be evaluated relative to the scope and objectives of this solicitation.

Submission Information

For this Program Announcement, the Project Description must be 25 pages or less, exclusive of attachments, and the proposal 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.

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.

Any recipient of an award from the Office of Science, performing research involving recombinant DNA molecules and/or organisms and viruses containing recombinant DNA molecules shall comply with the National Institutes of Health "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 instructions and format described below should be followed. Reference Program Announcement LAB 04-17 on all submissions and inquiries about this program.

OFFICE OF SCIENCE
GUIDE FOR PREPARATION OF SCIENTIFIC/TECHNICAL PROPOSALS TO BE SUBMITTED BY NATIONAL LABORATORIES

Proposals from National Laboratories submitted to the Office of Science (SC) as a result of this program announcement will follow the Department of Energy Field Work Proposal process with additional information requested to allow for scientific/technical merit review. The following

guidelines for content and format are intended to facilitate an understanding of the requirements necessary for SC to conduct a merit review of a proposal. Please follow the guidelines carefully, as deviations could be cause for declination of a proposal without merit review.

1. Evaluation Criteria

Proposals will be subjected to formal merit review (peer review) and will be evaluated against the following criteria which are listed in descending order of importance:

Scientific and/or technical merit of the project

Appropriateness of the proposed method or approach

Competency of the personnel and adequacy of the proposed resources

Reasonableness and appropriateness 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, the uniqueness of the proposer's capabilities, and demonstrated usefulness of the research for proposals in other DOE Program Offices as evidenced by a history of programmatic support directly related to the proposed work.

2. Summary of Proposal Contents

Field Work Proposal (FWP) Format (Reference DOE Order 5700.7C) (DOE ONLY)
Proposal Cover Page
Table of Contents
Abstract
Narrative
Literature Cited
Budget and Budget Explanation
Other support of investigators
Biographical Sketches
Description of facilities and resources
Appendix

2.1 Number of Copies to Submit

Formal proposals in response to Program Announcement LAB 04-17 are to be submitted as 2 paper copies of the proposal and one CD containing the proposal in PDF format. Color images should be submitted 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 hardcopies. They should be numbered and referred to in the body of the technical scientific proposal as Color image 1, Color image 2, etc.

3. Detailed Contents of the Proposal

Proposals must be readily legible, when photocopied, and must conform to the following three requirements: the height of the letters must be no smaller than 10 point with at least 2 points of spacing between lines (leading); the type density must average no more than 17 characters per inch; the margins must be at least one-half inch on all sides. Figures, charts, tables, figure legends, etc., may include type smaller than these requirements so long as they are still fully legible.

3.1 Field Work Proposal Format (Reference DOE Order 5700.7C) (DOE ONLY)

The Field Work Proposal (FWP) is to be prepared and submitted consistent with policies of the investigator's laboratory and the local DOE Operations Office. Additional information is also requested to allow for scientific/technical merit review.

Laboratories may submit proposals directly to the SC Program office listed above. A copy should also be provided to the appropriate DOE operations office.

3.2 Proposal Cover Page

The following proposal cover page information may be placed on plain paper. No form is required.

Title of proposed project
SC Program announcement title
Name of laboratory
Name of principal investigator (PI)
Position title of PI
Mailing address of PI
Telephone of PI
Fax number of PI
Electronic mail address of PI
Name of official signing for laboratory*
Title of official
Fax number of official
Telephone of official
Electronic mail address of official
Requested funding for each year; total request
Use of human subjects in proposed project:
If activities involving human subjects are not planned at any time during the proposed project period, state "No"; otherwise state "Yes", provide the IRB Approval date and Assurance of Compliance Number and include all necessary information with the proposal should human subjects be involved.
Use of vertebrate animals in proposed project:
If activities involving vertebrate animals are not planned at any time during this project, state "No"; otherwise state "Yes" and provide the IACUC Approval date and Animal Welfare Assurance number from NIH and include all necessary information with the proposal.

Signature of PI, date of signature
Signature of official, date of signature*

*The signature certifies that personnel and facilities are available as stated in the proposal, if the project is funded.

3.3 Table of Contents

Provide the initial page number for each of the sections of the proposal. Number pages consecutively at the bottom of each page throughout the proposal. Start each major section at the top of a new page. Do not use unnumbered pages and do not use suffices, such as 5a, 5b.

3.4 Abstract

Provide an abstract of no more than 250 words. Give the broad, long-term objectives and what the specific research proposed is intended to accomplish. State the hypotheses to be tested. Indicate how the proposed research addresses the SC scientific/technical area specifically described in this announcement.

3.5 Narrative

The narrative comprises the research plan for the project and is limited to 5 pages per task. It should contain the following subsections:

Background and Significance: Briefly sketch the background leading to the present proposal, critically evaluate existing knowledge, and specifically identify the gaps which the project is intended to fill. State concisely the importance of the research described in the proposal. Explain the relevance of the project to the research needs identified by the Office of Science. Include references to relevant published literature, both to work of the investigators and to work done by other researchers.

Preliminary Studies: Use this section to provide an account of any preliminary studies that may be pertinent to the proposal. Include any other information that will help to establish the experience and competence of the investigators to pursue the proposed project. References to appropriate publications and manuscripts submitted or accepted for publication may be included.

Research Design and Methods: Describe the research design and the procedures to be used to accomplish the specific aims of the project. Describe new techniques and methodologies and explain the advantages over existing techniques and methodologies. As part of this section, provide a tentative sequence or timetable for the project.

Subcontract or Consortium Arrangements: If any portion of the project described under "Research Design and Methods" is to be done in collaboration with another institution, provide information on the institution and why it is to do the specific component of the project. Further information on any such arrangements is to be given in the sections "Budget and Budget Explanation", "Biographical Sketches", and "Description of Facilities and Resources".

3.6 Literature Cited

List all references cited in the narrative. Limit citations to current literature relevant to the proposed research. Information about each reference should be sufficient for it to be located by a reviewer of the proposal.

3.7 Budget and Budget Explanation

A detailed budget is required for the entire project period, which normally will be three years, and for each fiscal year. It is preferred that DOE's budget page, Form 4620.1 be used for providing budget information*. Modifications of categories are permissible to comply with institutional practices, for example with regard to overhead costs.

A written justification of each budget item is to follow the budget pages. For personnel this should take the form of a one-sentence statement of the role of the person in the project. Provide a detailed justification of the need for each item of permanent equipment. Explain each of the other direct costs in sufficient detail for reviewers to be able to judge the appropriateness of the amount requested.

Further instructions regarding the budget are given in section 4 of this guide.

* Form 4620.1 is available at web site: http://www.sc.doe.gov/production/grants/Forms-E.html

3.8 Other Support of Investigators

Other support is defined as all financial resources, whether Federal, non-Federal, commercial or institutional, available in direct support of an individual's research endeavors. Information on active and pending other support is required for all senior personnel, including investigators at collaborating institutions to be funded by a subcontract. For each item of other support, give the organization or agency, inclusive dates of the project or proposed project, annual funding, and level of effort devoted to the project.

3.9 Biographical Sketches

This information is required for senior personnel at the laboratory submitting the proposal and at all subcontracting institutions. The biographical sketch is limited to a maximum of two pages for each investigator.

3.10 Description of Facilities and Resources

Describe briefly the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe pertinent capabilities, including support facilities (such as machine shops) that will be used during the project. List the most important equipment items already available for the project and their pertinent capabilities. Include this information for each subcontracting institution, if any.

3.11 Appendix

Include collated sets of all appendix materials with each copy of the proposal. Do not use the appendix to circumvent the page limitations of the proposal. Information should be included that may not be easily accessible to a reviewer.

Reviewers are not required to consider information in the Appendix, only that in the body of the proposal. Reviewers may not have time to read extensive appendix materials with the same care as they will read the proposal proper.

The appendix may contain the following items: up to five publications, manuscripts (accepted for publication), abstracts, patents, or other printed materials directly relevant to this project, but not generally available to the scientific community; and letters from investigators at other institutions stating their agreement to participate in the project (do not include letters of endorsement of the project).

4. Detailed Instructions for the Budget

(DOE Form 4620.1 "Budget Page" may be used)

4.1 Salaries and Wages

List the names of the principal investigator and other key personnel and the estimated number of person-months for which DOE funding is requested. Proposers should list the number of postdoctoral associates and other professional positions included in the proposal and indicate the number of full-time-equivalent (FTE) person-months and rate of pay (hourly, monthly or annually). For graduate and undergraduate students and all other personnel categories such as secretarial, clerical, technical, etc., show the total number of people needed in each job title and total salaries needed. Salaries requested must be consistent with the institution's regular practices. The budget explanation should define concisely the role of each position in the overall project.

4.2 Equipment

DOE defines equipment as "an item of tangible personal property that has a useful life of more than two years and an acquisition cost of $25,000 or more." Special purpose equipment means equipment which is used only for research, scientific or other technical activities. Items of needed equipment should be individually listed by description and estimated cost, including tax, and adequately justified. Allowable items ordinarily will be limited to scientific equipment that is not already available for the conduct of the work. General purpose office equipment normally will not be considered eligible for support.

4.3 Domestic Travel

The type and extent of travel and its relation to the research should be specified. Funds may be requested for attendance at meetings and conferences, other travel associated with the work and subsistence. In order to qualify for support, attendance at meetings or conferences must enhance

the investigator's capability to perform the research, plan extensions of it, or disseminate its results. Consultant's travel costs also may be requested.

4.4 Foreign Travel

Foreign travel is any travel outside Canada and the United States and its territories and possessions. Foreign travel may be approved only if it is directly related to project objectives.

4.5 Other Direct Costs

The budget should itemize other anticipated direct costs not included under the headings above, including materials and supplies, publication costs, computer services, and consultant services (which are discussed below). Other examples are: aircraft rental, space rental at research establishments away from the institution, minor building alterations, service charges, and fabrication of equipment or systems not available off- the-shelf. Reference books and periodicals may be charged to the project only if they are specifically related to the research.

a. Materials and Supplies

The budget should indicate in general terms the type of required expendable materials and supplies with their estimated costs. The breakdown should be more detailed when the cost is substantial.

b. Publication Costs/Page Charges

The budget may request funds for the costs of preparing and publishing the results of research, including costs of reports, reprints page charges, or other journal costs (except costs for prior or early publication), and necessary illustrations.

c. Consultant Services

Anticipated consultant services should be justified and information furnished on each individual's expertise, primary organizational affiliation, daily compensation rate and number of days expected service. Consultant's travel costs should be listed separately under travel in the budget.

d. Computer Services

The cost of computer services, including computer-based retrieval of scientific and technical information, may be requested. A justification based on the established computer service rates should be included.

e. Subcontracts

Subcontracts should be listed so that they can be properly evaluated. There should be an anticipated cost and an explanation of that cost for each subcontract. The total amount of each subcontract should also appear as a budget item.

4.6 Indirect Costs

Explain the basis for each overhead and indirect cost. Include the current rates.