

Program Announcement To DOE National Laboratories

LAB 00-20

Medical Applications Program

The Office of Biological and Environmental Research (OBER) of the Office of Science (SC), U.S. Department of Energy (DOE), hereby announces its interest in receiving proposals to support one specific research area within the Medical Applications Program: **Innovative approaches to cell-targeted ablation therapy for cancer with in vivo radiation techniques.** The emphasis will be on the therapeutic use of ionizing radiation such as may be achieved with radionuclide therapy or dual step techniques such as boron neutron capture therapy. The specific goals include development of novel ligands and delivery techniques to target and treat cancer at the cellular level. Special consideration will be given to proposals reflecting a well integrated, multidisciplinary team effort of scientists with skills to address such complex challenges as chemical ligand synthesis, tumor targeting, and dosimetry. Access to appropriate tumor models for pre-clinical testing will impact funding considerations. Proposals for clinical trials using already developed compounds and techniques will not be considered.

The Medical Applications Program supports directed nuclear medicine research in the areas of radiopharmaceutical development, molecular nuclear medicine and medical imaging to promote the use of radioisotopes for non-invasive diagnosis and therapy. Selective molecular targeting with radioligands will facilitate the analysis of cellular and tissue function and may enable purposeful disruption of specific cellular functions in tissues requiring therapy. The in-vivo distribution of radiopharmaceuticals and other cell-directed ligands may be defined and monitored with a variety of in-vivo imaging methods, such as the use of gamma cameras, positron emission tomographs (PET), fluorescent techniques and a variety of optical techniques. The development of in-vivo imaging techniques based on cell-targeting should assist reliable differentiation between normal and abnormal tissues at the molecular and/or metabolic levels, ideally leading to the development of more effective therapies and useful monitoring techniques for such therapies. Thus, highly selective substrate-binding molecules, when labeled with high energy-emitting radioisotopes or other noxious or pre-sensitizing agents, can become powerful tools for targeted molecular therapy of cancer.

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 molecular precision, recognition, and target selectivity. The availability of new

technology for high resolution imaging of small animals should facilitate the evaluation of new molecular ligands for their potential value and subsequent use in human trials of cancer therapy.

This Announcement is to solicit proposals for developing innovative approaches to cell-targeted ablation therapy for tumors with in vivo radiation techniques. A well integrated team effort by scientists from overlapping disciplines of chemistry, radiopharmaceutical chemistry, cellular and molecular biology, and biological and nuclear medicine imaging will be judged important in the evaluation of submitted research proposals. Methodological approaches that can be adapted to deliver more than one type of radiation or more than one radioisotope to the target sites are encouraged. It will be important for each proposal to consider also the following objectives:

- 1) Techniques to ensure highly selective tumor targeting by the proposed ligands;
- 2) Efficient screening techniques for selecting candidate ligands for in-vivo testing;
- 3) Preliminary data indicating reasonable likelihood of success for in-vivo targeting of primary tumors and their metastases in pre-clinical animal trials;
- 4) Reliable approaches for dosimetry calculations to normal tissues and to tumor sites based on 3-dimensional modeling;
- 5) Measurement techniques for accurately assessing the success of tumor targeting in vivo;
- 6) Measurement techniques for assessing therapy effects in vivo at the molecular, cellular and metabolic levels.

Program Funding

It is anticipated that up to \$2 million will be available for multiple awards in Fiscal Year 2001 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. Similar award sizes are anticipated for new 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.

Pre-proposals

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

DATES: Before preparing a formal proposal, potential proposers are encouraged to submit a brief pre-proposal. All pre-applications referencing Program Notice 00-20, should be received by DOE by 4:30 p.m., E.D.T., October 16, 2000. 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., E.S.T., January 5, 2001, to be accepted for merit review and consideration of an award in Fiscal Year 2001.

ADDRESSES: Pre-proposals referencing Program Announcement LAB 00-20, are to be sent, if possible, by E-mail or Fax to Ms. Sharon Betson (sharon.betson@science.doe.gov; Fax: 301-903-0567). Pre-proposals 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 referencing Program Announcement LAB 00-20, should be forwarded to: U.S. Department of Energy, Office of Science, Medical Sciences Division, SC-73, 19901 Germantown Road, Germantown, MD 20874-1290, ATTN: Program Announcement LAB 00-20. This address must also be used when submitting proposals by U.S. Postal Service Express Mail or any other commercial overnight delivery service, or hand-carried by the proposer. An original and seven copies of the proposal must be submitted.

FOR FURTHER INFORMATION CONTACT: Peter T. Kirchner, MD, or 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) 903-3213, FAX: (301) 903-0567, E-mail: peter.kirchner@science.doe.gov or prem.srivastava@science.doe.gov.

Submission Information

DOE is under no obligation to pay for any costs associated with the preparation or submission of proposals if an award is not made. In addition, in response to this 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 proposers 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 SC 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 instructions and format described below should be followed. Reference Program Announcement LAB 00-20 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

An original and seven copies of the formal proposal/FWP must be submitted.

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 25 pages. 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.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 \$5000 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.