Program Announcement To DOE National Laboratories
LAB 00-13
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: Imaging Gene Expression in Health and Disease. The specific goals include development of nuclear medicine driven technologies to image mRNA transcripts in real time in tissue culture and whole animals. Special consideration will be given to proposals arising from a well integrated, multidisciplinary team effort of scientists with skills to address the needs, issues and importance of nucleic acid biochemistry, radioligand synthesis and macromolecular interactions; functional consequences of gene expression by targeting and perturbing the activity of a particular gene; and biological applications of optical and radionuclide imaging devices; contributing to the goal of imaging specific gene expression in real time in animals to humans. The access to, or availability of specialized molecular radioligands, transgenic animal models of human disease, and biological imaging devices for real time imaging in animals to humans, will be important factors for funding considerations. Methodological approaches that are applicable to any mRNA species are encouraged.

The Medical Applications Program supports directed nuclear medicine research through radiopharmaceutical development, molecular nuclear medicine and medical imaging instrumentation program activities to study uses of radioisotopes for non-invasive diagnosis and internal molecular radiotherapy. Molecules directing or affected by homeostatic controls always interact and, thus, are targets for specific molecular substrates. The substrate molecules can be tailored to fulfil a specific need and labeled with appropriate radioisotopes to become measurable in real time in the body on their way to, and in interaction with their targets allowing the analysis of molecular function in homeostatic control in health and disease. The function of radiopharmaceuticals at various sites in the body is imaged by nuclear medical instruments, such as, gamma cameras and positron emission tomographs (PET). This type of imaging refines diagnostic differentiation at molecular/metabolic levels between health and disease, and among various diseases such as of the heart, brain and cancer, often leading to more effective therapy. If labeled with high energy-emitting radioisotopes, the substrate molecules, carrying the radiation dose may be powerful tools for targeted molecular therapy especially of cancer.

Basic research in molecular biology has provided new insights to the molecular basis of disease and molecular targets of human diseases. The current Molecular Nuclear Medicine program encourages development of new technologies for molecular delivery of radioisotopes to the disease-target-sites with a high degree of molecular precision, recognition, and target selectivity.

In addition nuclear medicine, with the availability of miniaturized PET technology for small animal imaging, can facilitate mapping of the biochemistry of the metabolic organ function, visualizing the molecular biology of cell function, and zooming in on gene function for delineating differences in molecular biology of normal health from disease, in animals to humans.

With the advent of the genome project and the development of transgenic mice, there has been a rapid proliferation of small animal models of human diseases, and improvement in optical and radionuclide in vivo imaging instrumentation technologies. These technological advancements have offered a paradigm shift in the current level of nuclear medicine research challenges and opportunities. Nuclear medicine techniques can permit analysis of the molecular elements as markers of genetic manipulations, biological transformations and progression of the disease, and provide insights to molecular pathways of disease and gene function. The development of generic methods to image specific gene expression will result in major advances in our understanding of developmental biology, cancer induction and pathogenesis, and in the clinical detection of inherited and acquired diseases. Such studies are therefore a major focus of this program. Additional information can be obtained at the following web site http://www.sc.doe.gov/production/ober/msd_reports.html.

This Announcement is to solicit proposals for imaging gene expression in real time, in tissue culture and in whole animals in vivo. Currently the expression of endogenous genes in animals (including humans) cannot be imaged, at least not directly. Given the astounding pace of biotechnology development, it may be highly challenging but not an unattainable goal. A well integrated concerted team effort from the overlapping disciplines of chemistry and radiopharmaceutical chemistry, cellular and molecular biology, and biological and nuclear medicine imaging will become increasingly important for success. It will be important for each proposal to address response in view of the following research areas, which may be crucial for progress in imaging gene expression:

1) The radioligand molecules that will interact with the macromolecular nucleic acid structures in vivo. For example, the advances in antisense drug discovery means that antisense radiopharmaceuticals through combinatorial chemistry techniques can be designed to hybridize to target transcripts in a highly specific way. However, the antisense and combinatorial molecular chemistry technologies available for chemotherapeutic drug development, must be fully exploited and optimized for in vivo imaging.

2) Molecular signal amplification methods are not yet available that work in vivo at the mRNA level, and technological advancement in this area is well desired.

3) Equally important is the hurdle of drug targeting technology, which must be developed to such an extent that the various biological barriers can be safely surmounted in vivo.

Finally, the fluorescent molecular imaging technologies available for more routine in vitro screening and in vivo real time imaging, that can be used as a proof of principle and a prelude to in vivo nuclear medicine imaging, should be exploited in conjunction with nuclear medicine devices.

Program Funding

It is anticipated that up to $1.5 million will be available for multiple awards during Fiscal Years 2000 and 2001 contingent upon the availability of appropriated funds. Previous awards have

ranged from $200,000 per year up 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 funds, progress of the research and programmatic needs.

DATES: Before preparing a formal proposal, potential proposers are encouraged to submit a brief preproposal. All preproposals referencing Program Announcement LAB 00-13, should be received by DOE by 4:30 p.m., E.D.T., April 14, 2000. A response encouraging or discouraging the submission of a formal proposal will be communicated by electronic mail by April 21, 2000.

Formal proposals submitted in response to this Announcement must be received by 4:30 p.m., E.D.T., May 30, 2000, to be accepted for merit review and consideration for award in Fiscal Years 2000 and 2001.

ADDRESSES: Preproposals referencing Program Announcement LAB 00-13, must be sent by E-mail to sharon.betson@science.doe.gov. 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 referencing Program Announcement LAB 00-13, should be forwarded to: U.S. Department of Energy, Office of Science, Office of Biological and Environmental Research, SC-73, 19901 Germantown Road, Germantown, MD 20874-1290, ATTN: Program Announcement LAB 00-13. 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 applicant. An original and seven copies of the proposal must be submitted.

FOR FURTHER INFORMATION CONTACT: Dr. Prem C. Srivastava, 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.

A brief preproposal should be submitted. The preproposal should identify, on the cover sheet, the title of the project, the institution, principal investigator name, address, telephone, fax, and E-mail address. The preproposal should consist of two to three pages identifying and describing the research objectives, methods for accomplishment, and the key members of the scientific team responsible for undertaking this effort. Preproposals will be evaluated relative to the scope and research needs for the Imaging Gene Expression Program.

In addition, for 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 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 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 00-13 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.