Program Announcement
To DOE National Laboratories
LAB 03-14

Radiopharmaceutical and Molecular Nuclear Medicine Science Research - Medical Applications Program

SUMMARY: 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 for research to support DOE/OBER Medical Applications Program areas in radiopharmaceuticals and molecular nuclear medicine. These program areas involve multifunctional, highly designed tracer molecules for precise in vivo tagging and noninvasive imaging assay of cellular and subcellular elements at the dynamic organ function, onset and progression of disease, and response to successful or failing therapy.

Research areas of particular programmatic interest include:

1. New tracer technologies for real-time, in vivo imaging of gene expression in health and disease.
2. New radiotracer labeling of progenitor cells for noninvasively imaging and tracking their behavior and fate in vivo and their overall role in organ and tissue regeneration in disease states.
3. New radiotracers for in vivo targeting of mutated proteins critical to carcinogenesis and tumor cell growth.
4. New generation of radiotracers enabling in vivo imaging assay of neurotransmitter chemistry and brain function.

DATES: Preproposals (letters of intent), including information on collaborators, and a one-page summary of the proposed research, should be submitted by **January 2, 2003**.

Formal proposals submitted in response to this solicitation must be received by 4:30 p.m., E.S.T., **Monday, February 24, 2003**, in order to be accepted for merit review and to permit timely consideration for award in Fiscal Year 2003.

ADDRESSES: Preproposals referencing Program Announcement LAB 03-14, should be sent to Ms. Sharon Betson by E-mail: sharon.betson@science.doe.gov, with a copy to Dr. Prem C. Srivastava at: prem.srivastava@science.doe.gov.

Formal proposals in response to this solicitation are to be submitted as PDF files on CDs. Three CDs should be submitted for each proposal. 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 them. They should be numbered and referred to in the body of the technical scientific proposal as Color image 1, Color image 2, etc.

The CDs, referencing Program Announcement LAB 03-14, should be sent to: Medical Sciences Division, SC-73/Germantown Building, Office of Biological and Environmental Research, Office of Science, U.S. Department of Energy, 1000 Independence Avenue, SW, Washington, D.C. 20585-1290, ATTN: Program Announcement LAB 03-14.

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: Medical Sciences Division, SC-73, Office of Biological and Environmental Research, Office of Science, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290, ATTN: Program Announcement LAB 03-14.

FOR FURTHER INFORMATION CONTACT: Dr. Prem C. Srivastava, Office of Biological and Environmental Research, Medical Sciences Division, U.S. Department of Energy, SC-73/Germantown Building, 1000 Independence Avenue SW, Washington, DC 20585-1290, Telephone: (301) 903-4071, FAX: (301) 903-0567, E-mail: prem.srivastava@science.doe.gov.

SUPPLEMENTARY INFORMATION: For over 50 years, the Department's Office of Science and its predecessors have supported basic physical science research for meeting the Nation's defense and security needs. The SC's Office of Biological and Environmental Research program has served as the Department's primary research arm for addressing the health and environmental consequences and potential public pay-offs of atomic energy explorations and use by translating the fundamental energy science to basic technology innovations and development for medical applications. Along the way, the OBER's Medical Applications program has leveraged the Department's unique capabilities in radiation chemistry, physics, engineering, computation, and biology, together with capabilities in and responsibilities for radiation detection and nuclear materials to support basic, high-risk research that today provides the upstream basis to use radiation and other energy technologies in medicine.

The mission of the OBER Medical Applications subprogram is to deliver relevant scientific knowledge that will lead to innovative diagnostic and treatment technologies for human health. The basic research technologies growing out of this program offer applications for noninvasive detection, diagnosis and early intervention of natural causes of disease, as well as of human-health-risks associated with the exposure of chemical, biological and nuclear material.

The modern era of nuclear medicine is an outgrowth of the original charge of the Atomic Energy Commission (AEC), "to exploit nuclear energy to promote human health." Today the program through radiopharmaceutical, molecular nuclear medicine and multimodal imaging systems research, seeks to develop new applications of radiotracers and radionuclide detectors in diagnosis and treatment by integrating the latest concepts and developments in chemistry, pharmacology, genomic sciences and transgenic animal models, structural, computational and molecular biology, and instrumentation.

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 targeted, 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 fulfill 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, often leading to more effective therapy.

Basic research in molecular biology has provided new insights to the molecular basis of disease and molecular targets of human diseases. The current Radiopharmaceutical and Molecular Nuclear Medicine programs encourage development of new generation of radiolabeled molecules and technologies for molecular delivery of radioisotopes to the disease-target-sites with a high degree of 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 instrumentation technologies for in vivo optical and radionuclide imaging. These technological advancements have offered a paradigm shift in the current level of nuclear medicine research challenges and opportunities. It is expected that radiopharmaceutical and molecular nuclear medicine techniques will permit analysis of the molecular elements as markers of genetic manipulations, biological transformations and progression of the disease, and will provide insights to molecular pathways of disease and gene function.

This Announcement is to solicit proposals for awards in any of the four research areas of interest to OBER Medical Applications program listed above.

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 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 one of the major focus areas of this program. Currently the expression of endogenous genes in animals (including humans) cannot be imaged, at least not directly. A well integrated team effort from the overlapping disciplines of chemistry and radiopharmaceutical chemistry, cellular and molecular biology, and biological and nuclear medicine imaging will be increasingly important. 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) New generation of radioligand molecules that will interact with the macromolecular nucleic acid structures in vivo.

2) Molecular technologies which will significantly improve the signal to background ratio and will make in vivo imaging feasible. 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.

4) 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.

Radiopharmaceutical research for Noninvasive Radiotracer-cell Imaging (NRI) In Vivo:

Progenitor Cells: The term progenitor cells implies non-embryonic stem cells, and does **not** include embryonic stem cells. For definitions, refer to National Institutes of Health (NIH) web sites, and all researchers must adhere to federal guidelines when involving human subjects. http://www.nih.gov/news/stemcell/primer.htm and http://www.nih.gov/news/stemcell/index.htm.

Breakthrough research in the biology of inter-organ and tissue cell repopulation and transformation has offered new paradigms for radiotracer imaging research in resolving the issues of progenitor cell administration including their trafficking, biodistribution, fate and progeny in organ and tissue regeneration, repair and replacement, with wide applications to human disease states such as neurogenesis, myogenesis, hematopoiesis, including stroke, ischemic heart disease, Parkinson's disease, hematopoetic disorders and cancers. This NRI specific program announcement offers challenging research opportunities for new radiotracer technology innovations for emerging new clinical research needs and medical applications.

The specific goals include radiotracer labeling of progenitor cells for noninvasively imaging and tracking their behavior and fate in vivo and their overall role in organ and tissue regeneration in disease states. The researchers should clearly demonstrate the relevance and important clinical need of the research proposed. Special consideration will be given to proposals arising from a well-integrated, multidisciplinary team effort of scientists with relevant skills in radiopharmaceutical chemistry, biology, pharmacology and clinical nuclear medicine. The access to, or availability of specialized radiotracer-labeling and imaging instrumentation, equipment and facilities for real time imaging in animals to humans, will be important factors for funding considerations.

New radiotracers for targeting mutated proteins critical to carcinogenesis and tumor cell growth:

Radiolabeled molecular probes for targeting protein mutations critical to carcinogenesis and tumor cell growth would be unique tools for in vivo measuring of kinase pathways, for early diagnosis of cancer, for monitoring cancer therapy, and for understanding the mechanism of action of drugs targeting protein kinase activity in the development of new therapeutic drugs. Important therapeutic agents are being developed based on their specificity for protein kinases critically involved in intracellular signaling pathways, and there are likely to be about two thousand protein kinases encoded by the human genome. In recent years several small molecules have been identified to exhibit high degree of specificity for particular protein kinases, and a myriad of other compounds have also been identified as inhibitors of receptor tyrosine kinases and of mitogen-activated protein kinase cascades. Interaction of these compounds with these key kinases results in blockade of signal transduction and inhibition of cell cycle progression. This knowledge has resulted in the discovery of molecules with high specificity for several protein kinases and has provided a new view to cancer treatment. It also provides a challenging perspective for in vivo quantification of these intracellular pathways controlling cell proliferation and critically involved in cancer progression.

The Department, through its synchrotron light sources facilities, contributes significantly to genomics/proteomics, i.e. protein analysis and structural genomics, and allows the structural biologists to find the specific parts of the protein structure that are most vulnerable to drugs or that may be key to carcinogenesis. The Department's investments in biophysics, chemistry, robotics and supercomputing, have made it possible to rapidly investigate the detailed arrangements of atoms and understand the function of thousands of proteins whose structures are coded by the genome of animals, bacteria and plants. Harnessing of the structural genomics/proteomics information will be a key to designing new small radiotracer molecules for precisely targeting the vulnerable areas of a mutated protein structure expressing cancer. Radiotracer molecules like these will be useful in laboratory investigations, and validation as molecular imaging probes for early diagnosis of cancer and management of cancer therapeutics.

New generation of radiotracers enabling in vivo imaging assay of neurotransmitter chemistry and brain function: New generation of highly innovative and target specific radiotracer molecules are required as diagnostic markers for noninvasively imaging the regional biochemistry associated with metabolic organ function and performance, for guiding surgery, and for guiding new drug development.

Program Funding

It is anticipated that up to $2 million will be available for multiple awards during Fiscal Year 2003, contingent upon the availability of appropriated funds. Previous awards have ranged from $200,000 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.

Preproposals

A brief preproposal (letter of intent) should be submitted. The preproposal should identify, on the cover sheet, the title of the project, the institution, principal investigator's name, address, telephone, fax, and E-mail address. The preproposal should consist of one to two pages identifying and describing the research objectives, methods for accomplishment, and the key members of the scientific team responsible for undertaking this effort, including information on collaborators. Preproposals will be evaluated relative to the scope and programmatic research needs.

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, for this Solicitation, the Project Description must be 20 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. Also provide 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. 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 03-14 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. (Unless otherwise instructed in this Program Announcement.)

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 $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.