

**Office of Science
Notice 03-14**

***Radiopharmaceutical and Molecular
Nuclear Medicine Science Research -
Medical Applications Program***

Department of Energy

Office of Science Financial Assistance Program Notice 03-14: Radiopharmaceutical and Molecular Nuclear Medicine Science Research - Medical Applications Program

AGENCY: U.S. Department of Energy

ACTION: Notice inviting grant applications.

SUMMARY: The Office of Biological and Environmental Research (OBER) of the Office of Science (SC), U.S. Department of Energy (DOE), hereby announces its interest in receiving grant applications 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: Preapplications (letters of intent), including information on collaborators, and a one-page summary of the proposed research, should be submitted by **January 2, 2003**.

Formal applications submitted in response to this notice 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: Preapplications referencing Program Notice 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 applications in response to this solicitation are to be electronically submitted by an authorized institutional business official through DOE's Industry Interactive Procurement System (IIPS) at: <http://e-center.doe.gov/>. IIPS provides for the posting of solicitations and receipt of applications in a paperless environment via the Internet. In order to submit applications through IIPS your business official will need to register at the IIPS website. The Office of Science will include attachments as part of this notice that provide the appropriate forms in PDF fillable format that are to be submitted through IIPS. Color images should be submitted in IIPS as a separate file in PDF format and identified as such. These images should be kept to a minimum due to the limitations of reproducing them. They should be numbered and referred to in the body of the technical scientific application as Color image 1, Color image 2, etc. Questions regarding the operation of IIPS may be E-mailed to the IIPS Help Desk at: HelpDesk@pr.doe.gov or you may call the help desk at: (800) 683-0751. Further information on the use of IIPS by the Office of Science is available at: <http://www.sc.doe.gov/production/grants/grants.html>.

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

FOR FURTHER INFORMATION CONTACT: 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. The full text of Program Notice 03-14 is available via the Internet using the following web site address: <http://www.sc.doe.gov/production/grants/Fr03-14.html>.

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 Notice is to solicit applications for grants 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 applications 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 application 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 grantees 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, hematopoietic 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 applications 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 \$4 million will be available for multiple grant 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 grants. Applications 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.

Preapplications

A brief preapplication (letter of intent) should be submitted. The preapplication 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 preapplication 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. Preapplications will be evaluated relative to the scope and programmatic research needs.

Merit Review

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

1. Scientific and/or Technical Merit of the Project;
2. Appropriateness of the Proposed Method or Approach;
3. Competency of Applicant's Personnel and Adequacy of Proposed Resources;
4. 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 and the agency's programmatic needs. Note, external peer reviewers are selected with regard to both their scientific expertise and the absence of conflict-of-interest issues. Non-federal reviewers may be used, and submission of an application constitutes agreement that this is acceptable to the investigator(s) and the submitting institution.

Submission Information

Information about the development, submission of applications, eligibility, limitations, evaluation, the selection process, and other policies and procedures may be found in 10 CFR Part 605, and in the Application Guide for the Office of Science Financial Assistance Program. Electronic access to the Guide and required forms is made available via the World Wide Web at: <http://www.sc.doe.gov/production/grants/grants.html>. DOE is under no obligation to pay for any costs associated with the preparation or submission of applications if an award is not made.

In addition, for this Notice, the Project Description must be 20 pages or less, exclusive of attachments, and the application must contain a Table of Contents, an abstract or project summary, letters of intent from collaborators (if any), and short curriculum vitae consistent with National Institutes of Health guidelines. On the SC grant face page, form DOE F4650.2, in block 15, 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.

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

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

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Associate Director of Science
for Resource Management

Published in the Federal Register November 22, 2002, Volume 67, Number 226, Pages 70417-70420.