

Office of Science
Notice 00-13

Medical Applications Program

Department of Energy
Office of Science

Office of Science Financial Assistance Program Notice 00-13; Medical Applications Program

AGENCY: U.S. Department of Energy (DOE)

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 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 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.

DATES: Before preparing a formal application, potential applicants are encouraged to submit a brief preapplication. All preapplications referencing Program Notice 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 application will be communicated by electronic mail by April 21, 2000.

Formal applications submitted in response to this notice 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: Preapplications referencing Program Notice 00-13, must be sent by E-mail to sharon.betson@science.doe.gov. Preapplications 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 applications referencing Program Notice 00-13, should be forwarded to: U.S. Department of Energy, Office of Science, Grants and Contracts Division, SC-64, 19901 Germantown Road, Germantown, MD 20874-1290, ATTN: Program Notice 00-13. This address must also be used when submitting applications 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 application 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. The full text of Program Notice 00-13 is available via the Internet using the following web site address: <http://www.sc.doe.gov/production/grants/grants.html>.

SUPPLEMENTARY INFORMATION: 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 Notice is to solicit applications for grants 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 application 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.
- 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.

Program Funding

It is anticipated that approximately \$3 million will be available for multiple grant 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 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 should be submitted. The preapplication should identify, on the cover sheet, the title of the project, the institution, principal investigator name, address, telephone, fax, and E-mail address. The preapplication 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. Preapplications will be evaluated relative to the scope and research needs for the Imaging Gene Expression Program.

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 25 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.

John Rodney Clark
Associate Director of Science
for Resource Management

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