Office of Science
Financial Assistance
Funding Opportunity Announcement
DE-PS02-08ER08-11

Radiochemistry and Instrumentation Research

The Office of Biological and Environmental Research (BER) of the Office of Science (SC), U.S. Department of Energy (DOE), hereby announce its interest in receiving applications for pilot research project grants in two topic areas. **The first topic area is radiochemistry.** BER invites applications for conducting fundamental research in radiotracer chemistry, involving particularly improvements in the synthetic methodology for incorporating the radioisotope in a wide range of organic molecules with techniques that result in high specific activities and sufficient protections against auto-radiolysis to ensure the integrity and biological behavior of the intact radiolabeled molecule *in vivo*. **The second topic area is in imaging instrumentation.** BER invites applications dealing with the design and development of new, improved radionuclide imaging instrumentation that can significantly increase the accuracy of quantitative assessments of the three dimensional spatial and temporal distribution of radiotracers in living systems. Applications should focus on basic research that will significantly advance the current state of the science underpinning nuclear medicine advances.

Responses to this announcement should address the development and use of highly innovative radiotracer chemistry or instrumentation technologies for quantitative *in vivo* measurement of site-specific (*in situ*) chemical reactions, their metabolic perturbations, and ensuing biological processes with a high degree of specificity.

Program Funding

Total awards in Fiscal Year 2008 are anticipated to be up to $7,000,000 for radiochemistry research and up to $3,000,000 for imaging instrumentation research. The number of awards will be contingent on satisfactory peer review, the availability of appropriated funds, and the size of the awards. Individual grants will be available as one time awards for pilot research projects that may extend to two-years. Award requests for projects longer than one year should include one total budget (one budget page) for the entire project period. The total budget for a pilot research project is expected to be in the general range of $250,000 to $400,000 total costs (direct plus indirect) for one year, prorated for the actual length of the project. DOE is under no obligation to pay for any costs associated with the preparation or submission of an application. DOE reserves the right to fund, in whole or in part, any, all, or none of the applications submitted in response to this Notice.

PREAPPLICATIONS

Potential applicants are **strongly encouraged** to submit a brief preapplication, referencing Program Notice DE-PS02-08ER08-11 for receipt by DOE by 4:30 p.m., Eastern Time, **February 25, 2008.**

Preapplications are limited to **three pages total**, including cover page. The cover page should include the title of the project, the institution or organization, principal investigator name, telephone number, fax number, and e-mail address. Preapplications should be sent as a text file without attachments or a single PDF file attachment via e-mail to: **radiochem@science.doe.gov** with **"Preapplication DE-PS02-08ER08-11 - [Radiochemistry or Imaging Instrumentation]"** as the subject. No FAX or mail submission of preapplications will be accepted.

Preapplications will be reviewed for conformance with the guidelines presented in this Notice and suitability in the technical areas specified in this Notice. A response to the preapplications encouraging or discouraging formal applications will be communicated to the applicants by **March 10, 2008**. Applicants who have not received a response regarding the status of their preapplication by this date are responsible for contacting the program to confirm this status.

Preapplications should consist of no more than two pages of narrative stating the research objectives, describing the technical approach(s), and identifying the proposed team members and their expertise. No budget information or biographical data need be included, nor is an institutional endorsement necessary. The intent in requesting a preapplication is to save the time and effort of applicants in preparing and submitting a formal project application that may be inappropriate for the program.

APPLICATION DUE DATE: April 17, 2008, 8:00 pm, Eastern Time

Applications must be submitted using Grants.gov, the Funding Opportunity Announcement can be found using the CFDA Number, 81.049 or the Funding Opportunity Announcement number, DE-PS02-08ER08-11. Applicants must follow the instructions and use the forms provided on Grants.gov.

GENERAL INQUIRIES ABOUT THIS NOTICE SHOULD BE DIRECTED TO:

Agency Contact:

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SUPPLEMENTARY INFORMATION:

For over 50 years, one important focus of BER and its predecessor programs has been to promote research advances in physics, chemistry, material sciences and high speed computing to translate our knowledge of radioactive-decay and its detection into radiotracer imaging technology innovations for use in biomedical research . The radiotracer and radionuclide imaging technologies already developed under this program have been used to solve critical

problems in biology and nuclear medicine, and they constitute to form a large part of the scientific foundations of nuclear medicine today.

Along the way, advances in genomics, transgenic animal models and micro-imaging instrumentation technologies have prompted a paradigm shift from imaging human organ function in health and disease to directly visualizing *in vivo* metabolic networks and regulatory systems, their interaction with molecular elements, and the ensuing chemical reactions in biological processes that underlay the functional differentiation of organs, tissues and specialized cell types.

Molecules that either direct or are subject to homeostatic controls in biological systems are convenient targets for specific molecular substrates. Such target-directed substrates (molecular probes) can be tailored to reflect a specific molecular interaction. Labeled with appropriate radioisotopes these molecular probes can be measured *in vivo*, in real time, on their way to, and in interaction with their targets *in vivo*. In other words, they allow the quantitative measurement of selected molecular interactions during normal tissue homeostasis and again after perturbations of the normal state. The *in vivo* quantification of radiolabeled molecules at various regional sites is accomplished by specialized radiation imaging instruments, such as single photon emission computed tomographs (SPECT) and positron emission computed tomographs (PET). This type of imaging has the capability of differentiating biological processes at the molecular and the metabolic levels.

One of the most striking advantages of the *in vivo* radionuclide imaging techniques, when compared to other imaging modalities such as magnetic resonance imaging or X-ray computed tomography, is the sensitivity of the technique. In order to advance the current state of the science in nuclear medicine, this solicitation offers fundamental research opportunities in two topic areas, Radiochemistry and Imaging Instrumentation, as follows.

Radiochemistry: Radiolabeled probes (radiotracers) can be detected at concentrations up to 1000-fold lower than those labeled with non-radioactive markers (e.g. contrast agents). In order to best utilize this remarkable sensitivity for the study of low abundance targets of biological interest, one needs to maximize the specific activity of the radiolabeled molecular probe. Higher specific activity probes would allow for improved quantitative information about the target molecule and its binding capacity.

This Notice is to solicit applications for grants in the radiochemistry topic area to support development of new techniques for radiolabeling of molecular probes (including nanoparticles) of biological importance, with radionuclides currently available, in specific activities that approach the theoretical maximums for these specific probes. These new radiolabeling techniques should also incorporate preventive measures to protect the probe from auto-radiolysis in vitro and *in vivo*. These new labeling techniques can be applicable to molecular probes for either PET or SPECT imaging. This notice also solicits the development of techniques for linking two different imaging labels (e.g. two different radionuclides or one fluorescent- and radio-label) at two different sites of the same molecular probe for simultaneous quantitative assessment of two different biochemical reactions that may reflect two different functional characteristics or a combination of

structural and functional information through the use of multimodality/hybrid instruments such as PET/MRI, PET/CT or PET combined with an Optical detector system.

Radionuclide Imaging Instrumentation

There is an urgent need for high resolution and high sensitivity small PET scanners for radiotracer imaging in biology. These scanners are needed to study biochemical metabolism, to visualize the molecular biology of cell function, and to elucidate the gene expression of the cell type that governs functional differentiation of organs, tissues and specialized cell types.

To achieve these goals, improvements in instrumentation are needed to accurately quantify radiotracers present in low concentrations in small tissue volumes. In order to accomplish this goal, new developments, improvements or radical changes are needed in the fundamental detector components that are essential transmitters of quantitative information. These components include radiation sensors (scintillators, photodetectors, and solid-state detectors), electronics, and reconstruction and noise-reduction algorithms. It is often these fundamental components that limit the performance of current instruments.

This Notice solicits applications for grants to support development of new advanced instruments which can provide spatial/imaging resolution of less than 1 mm (ideally 500 mm or better) throughout the entire field of view, have sensitivities the same or significantly higher than currently available high-resolution MicroPET systems for *in vivo* radiotracer imaging in real-time.

General Requirement - Potential Applications and Benefits of Radiochemistry and Imaging Instrumentation in Biology Underpinning Major Advances in Nuclear Medicine: Within the context of the current mission, scope and focus of BER, the programmatic goal of this solicitation is to provide, through basic research, the Radiochemistry and Instrumentation capabilities for quantitative measurement, detection and study of *in situ* perturbations of homeostatic reactions and biological processes underlying the functional differentiation of organs, tissues and specialized cell types. It is anticipated that new radiotracer and new imaging instrumentation technologies will provide invaluable tools to investigators for advancing the biological applications of nuclear medicine.

Applications should address hypothesis-driven research to define and/or understand the key physical, chemical, and biological problems influencing the need for the proposed technological advance. Furthermore, these applications should discuss and detail the scientific basis for the development of new, innovative radiochemistry or imaging instrumentation technologies. **Applications should address the applicability of the proposed research to DOE's stated investments in science and technology and describe how the proposed research will contribute to the advancement of nuclear medicine.**

Biological targets included for the proof of concept to study potential applications of the investigative technologies under this Notice are listed below.

Endogenous Genes: Radiotracer technologies to image mRNA transcripts in real time in tissue culture and in animal models. These include new generation of radioligand molecules that will interact with the macromolecular nucleic acid structures *in vivo*, and technologies which will significantly improve the signal to background ratio and will make *in vivo* visualization of *in situ* chemical reactions and the effects of their perturbations feasible. Successful projects should contribute to the goal of imaging specific gene expression in real time *in vivo*.

Protein Structures: Radiolabeled molecular probes for targeting protein structures including mutations critical in mediating cellular signaling and developmental pathways to carcinogenesis and abnormal cell growth. Such radiolabeled probes would be unique tools for *in vivo* measurement of specific biological pathways, and for understanding the mechanism of action of target specific new drugs.

Cellular Targets of Low Abundance: Radiotracers for *in vivo* targeting and imaging sites in and/or on cells that allow those cells to respond to external or environmental stimuli including cell to cell communications, and to study progeny, behavior, fate and repopulation of highly specialized cell types in important biological processes.

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 Approach and Methods
3. Competency of the Research Team and Adequacy of Available Resources
4. Justification 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. It should be noted that external peer reviewers are selected on the basis of 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 review process is acceptable to the investigator(s) and the submitting institution.

Posted on the Office of Science Grants and Contracts Web Site
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