Office of Science
Financial Assistance
Funding Opportunity Announcement
DE-FOA-0000265

Radiochemistry and Radionuclide Imaging Instrumentation Research

SUMMARY:

The Office of Biological and Environmental Research (BER) of the Office of Science (SC), U.S. Department of Energy (DOE) advances world-class biological and environmental research programs and scientific facilities for DOE missions in energy, environment, and basic research. The Radiochemistry and Radionuclide Imaging Instrumentation Research program within BER, supports fundamental research for developing new methodologies for real-time, high-resolution imaging of dynamic biological processes in living systems. This research has two integrated goals: First, the research supports the DOE Science mission-related activities in bioenergy and bioremediation; Second, the fundamental methodologies developed under DOE-funded research may serve as tools leading to transformational new technologies for use in nuclear medicine research and applications supported by NIH and industry. Applicants are encouraged to meet these two goals. Responses to this Funding Opportunity Announcement (FOA) should address the development and use of highly innovative radiotracer chemistry or instrumentation technologies for quantitative *in vivo* measurement of site-specific chemical reactions, their spatial distributions and metabolic perturbations, and ensuing biological processes with a high degree of accuracy and sensitivity. BER hereby announces its interest in receiving applications for research grants in two topic areas, Radiochemistry and Radionuclide Imaging Instrumentation. **In the area of Radiochemistry**, BER invites applications for fundamental research to improve synthetic methodology for rapidly and efficiently incorporating radionuclides into a wide range of organic molecules. Approaches should use methods that allow dual or multiple labeling of targeting molecules for dual energy or hybrid imaging techniques in intact living systems and/or *in vivo* models. Development of microfluidics for synthesis and purification are also appropriate. **In the area of Radionuclide Imaging Instrumentation**, BER invites applications to design and develop new or improved radionuclide detection and imaging instrumentation. These improvements should significantly increase the accuracy of quantitative assessments of the three dimensional spatial and temporal distribution of radiotracers in living systems, allow the screening of large numbers of intact living systems (e.g. plants), or the screening of cells to identify desirable characteristics. Development of instruments which allow simultaneous examination of biological systems using different modalities to improve understanding is also encouraged.

Applications should focus on basic research that will significantly advance the current state of the science underpinning biological systems of importance to the mission of the DOE, and which may also have application in nuclear medicine.

PREAPPLICATIONS

Potential applicants are **REQUIRED** to submit a brief preapplication, referencing Funding Opportunity Announcement DE-FOA-0000265 for receipt by DOE by 4:30 p.m., Eastern Time, **March 9, 2010**. Preapplications will be reviewed for conformance with the guidelines presented in this FOA and suitability in the technical areas specified in this FOA. A response to the preapplications encouraging or discouraging formal applications will be communicated to the applicants by **March 16, 2010**. Applicants who have not received a response regarding the status of their preapplication by this date are responsible for contacting the program to confirm the status.

Only those preapplicants that receive notification from DOE encouraging a formal application may submit full applications. **No other formal applications will be considered**. Preapplications referencing Funding Opportunity Announcement DE-FOA-0000265 should be sent as PDF file attachments via e-mail to: radiochem@science.doe.gov with "Preapplication DE-FOA-0000265 - [indicating either Radiochemistry or Imaging Instrumentation depending upon the nature of the preaaplication]" as the subject. **No FAX or mail submission of preapplications will be accepted.**

Potential applicants must submit a brief preapplication that consists of 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 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 19, 2010, 11:59 p.m. Eastern Time

Formal applications submitted in response to this FOA must be received by April 19, 2010, 11:59 p.m. Eastern time, to permit timely consideration of awards. **APPLICATIONS RECEIVED AFTER THE DEADLINE WILL NOT BE REVIEWED OR CONSIDERED FOR AWARD.**

IMPORTANT SUBMISSION INFORMATION:

The full text of the Funding Opportunity Announcement (FOA) is located on FedConnect. Instructions for completing the Grant Application Package are contained in the full text of the FOA which can be obtained at: https://www.fedconnect.net/FedConnect/?doc=DE-FOA-0000265&agency=DOE. To search for the FOA in FedConnect click on "Search Public Opportunities". Under "Search Criteria", select "Advanced Options", enter a portion of the title "Radiochemistry and Radionuclide Imaging Instrumentation Research", then click on "Search". Once the screen comes up, locate the appropriate Announcement.

In order to be considered for award, Applicants must follow the instructions contained in the Funding Opportunity Announcement.

WHERE TO SUBMIT: Applications must be submitted through Grants.gov to be considered for award.

You cannot submit an application through Grants.gov unless you are registered. Please read the registration requirements carefully and start the process immediately. Remember you have to update your CCR registration annually. If you have any questions about your registration, you should contact the Grants.gov Helpdesk at 1-800-518-4726 to verify that you are still registered in Grants.gov.

Registration Requirements: There are several one-time actions you must complete in order to submit an application through Grants.gov (e.g., obtain a Dun and Bradstreet Data Universal Numbering System (DUNS) number, register with the Central Contract Registry (CCR), register with the credential provider, and register with Grants.gov). See http://www.grants.gov/GetStarted. Use the Grants.gov Organization Registration Checklist at http://www.grants.gov/assets/OrganizationRegCheck.pdf to guide you through the process. Designating an E-Business Point of Contact (EBiz POC) and obtaining a special password called an MPIN are important steps in the CCR registration process. Applicants, who are not registered with CCR and Grants.gov, should allow at least 21 days to complete these requirements. It is suggested that the process be started as soon as possible.

IMPORTANT NOTICE TO POTENTIAL APPLICANTS:
When you have completed the process, you should call the Grants.gov Helpdesk at 1-800-518-4726 to verify that you have completed the final step (i.e. Grants.gov registration).

Questions: Questions relating to the registration process, system requirements, how an application form works, or the submittal process must be directed to Grants.gov at 1-800-518-4726 or support@grants.gov. Part VII of the FOA explains how to submit other questions to the Department of Energy (DOE).

All applications should be in a single PDF file.

GENERAL INQUIRIES ABOUT THIS FOA SHOULD BE DIRECTED TO:

Technical/Scientific Program Contact:

Program Manager: Dr. Prem C. Srivastava
Office of Biological and Environmental Research
U. S. Department of Energy
Phone: 301-903-4071
E-Mail: Prem.Srivastava@science.doe.gov

SUPPLEMENTARY INFORMATION:

For over 60 years, an important focus of BER and its predecessor offices has been to promote research advances in physics, chemistry, material sciences and high speed computing to translate knowledge of radioactive-decay and its detection into innovative radiotracer imaging technology for use in biological and nuclear medicine 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 constitute 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 to directly visualizing *in vivo* metabolic networks and regulatory systems, their interaction with molecular probes, and the chemical reactions in biological systems that underlay the function of organs, tissues and specialized cell types. Although research into basic radiochemistry and instrumentation continues, the program focus has been realigned with the DOE mission to bring the fruits of this research to bear upon new imaging technologies for addressing biological research problems in plant biology related to biofuel production and in the study of microbial-communities related to bioremediation.

The current BER Radiochemistry and Radionuclide Imaging Instrumentation program supports fundamental radiochemistry and radionuclide imaging instrumentation research for metabolic imaging in living systems (e.g., plants). This research is intended to have an impact on DOE mission-related activities in bioenergy and bioremediation by developing new methodologies for real-time, high-resolution imaging of dynamic biological processes in energy- and environment-relevant contexts. These new methodologies are in fact intended to be widely applicable, including nuclear medicine research and applications supported by NIH and industry.

Molecules that either control or are controlled by dynamic equilibria adjustment and regulation mechanisms in biological systems are convenient targets for specific molecular probes. Such molecular probes can be tailored to target a specific molecular interaction and when labeled with appropriate radioisotopes allow the quantitative measurement of selected molecular interactions under normal conditions and after intervention or perturbation of the normal state. The *in vivo* quantification of radiolabeled molecules at various regional sites is accomplished by specialized radiation detection or imaging instruments, such as beta probes, single photon emission computed tomography (SPECT) systems and positron emission computed tomography (PET) systems. This approach has the capability of measuring biological processes at the molecular and the metabolic levels. One limitation of the imaging techniques is that the spatial resolution is somewhat limited. This can be substantially improved with hybrid imaging techniques as has been well demonstrated by PET-CT hybrid imaging. Another advantage to hybrid imaging is the possibility of measuring two different biochemical or metabolic processes at the same time. Hence the development of efficient approaches for dual labeling of molecular probes with maintenance of high specific activity for the radioactive label is highly desirable.

Radiochemistry: Radiolabeled probes (radiotracers) can be detected at concentrations up to 1000-fold lower than those labeled with non-radioactive markers. This remarkable sensitivity for the study of low abundance targets of biological interest requires a high specific activity of the

radiolabeled molecular probe. High specific activity probes generally allow improved quantitative information about the target molecule and its binding capacity.

This FOA is to solicit applications for grants in the radiochemistry topic area to support development of new innovative synthetic procedures for single labeling and techniques for dual labeling of molecular probes of biological importance. The dual labels can include modalities such as PET, SPECT, MR, optical and others in order to reflect two different functional characteristics or a combination of structural and functional information through the use of multimodality/hybrid instruments.

Basic radiochemistry studies to develop new radiolabeling techniques are highly desirable and important. For example, the most widely used radionuclide in nuclear medicine is fluorine-18, which has suitable properties for imaging of plant cellular metabolism and ligand-receptor interactions. Similarly, metals (e.g. copper, iron, or molybdenum) play a critical role in biological processes such as molecular signaling, gene expression, and enzyme activation and catalysis in all organisms. Therefore, it will be important to develop appropriate metal radioligands for imaging to study the roles of metals in biological systems. These new techniques should be generally applicable for radiotracer syntheses to produce a series of radiolabeled compounds in high radiochemical yields and in very high specific activity that are important for use in the various research fields of interest to DOE. Radiotracers needed for imaging biological processes and substances in living systems including those of interest to DOE (e.g.biofuel plants and microbial communities) encompass gene expression, enzyme actions, transport kinetics, metabolism, macromolecular interactions, symbiotic interactions, intracellular signal transduction and environmental sensing including cell to cell communication.

Radionuclide Imaging Instrumentation

There is an urgent need for design and development of new or improved radionuclide detection and imaging instrumentation that can significantly increase the accuracy of quantitative assessments of the three dimensional spatial and temporal distribution of radiotracers in living systems. This need is particularly applicable to the study of biological systems of interest to the DOE mission such as biofuel plants, but which also will have application in general biological imaging. The key improvements which are essential in the radiotracer detector implementation *in planta* are spatial resolution and sensitivity. Detector systems with greater sensitivity are especially desirable when limited by the amount and the binding affinity of the radiotracer probe introduced into the living biological system for *in vivo* imaging. Another goal of this program is the development of instruments that are capable of acquiring data from more than one modality simultaneously. Instruments where spatial resolution (using for example CT or MR) and high sensitivity (using for example PET or optical) are combined into an integrated system, are also desirable.

A final goal is the development of high throughput imaging techniques to quickly identify desirable metabolic or genetic characteristics. In order to accomplish these goals, new developments, improvements or radical changes are needed in the fundamental detector components that are necessary for simultaneous measurement of spatial, metabolic and biochemical data. Also desired are significant improvements and/or radical design changes for

effective combinations of signal detectors (scintillators, or solid-state detectors), electronics, signal processing and display systems, and new faster reconstruction, noise-reduction and modeling algorithms.

This FOA solicits applications for grants to support development of new advanced hybrid instruments which can provide accurate spatial localization and quantitative measurement of metabolic and biochemical processes in 1 mm3volumes throughout the entire field of view and have sensitivities the same or significantly higher than currently available high-resolution MicroPET or MicroSPECT systems.

General Requirement - Potential Applications and Benefits of Radiochemistry and Imaging Instrumentation in Biology Underpinning Major Advances in Nuclear Medicine: Within the context of BER's current mission, scope and focus, the programmatic goal of this FOA is to provide, through basic research, the Radiochemistry and Instrumentation capabilities for quantitative measurement, detection and study of biological processes. In addition to facilitating the development of new biofuels, it is anticipated that these new radiotracer and imaging instrumentation technologies will also 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 advances. Furthermore, these applications should discuss and detail the scientific basis for the development of new, innovative radiochemistry or imaging instrumentation technologies. Applications should describe plans to demonstrate the feasibility of the proposed research in a suitable biological system relevant to the DOE's mission needs, and describe how the proposed research will contribute to the advancement of nuclear medicine.

The proposed research is intended to fill critical knowledge gaps, including the exploration of some high-risk approaches. BER also encourages the submission of innovative "high-risk" applications with potential for future high impact on Radiochemistry and Radionuclide Imaging Instrumentation Research. The probability of success and the risk-reward balance will be considered when making funding decisions.

Collaboration

Multi-disciplinary and inter-institutional collaborations are strongly encouraged to enhance and strengthen research capabilities as needed. Collaboration could include institutions such as universities, industry, non-profit organizations, federal laboratories and Federally Funded Research and Development Centers (FFRDCs), including the DOE National Laboratories (DOE Labs). All collaborative applications should include letters of agreement from each collaborator who would receive funding. These letters should specify the contributions the collaborators intend to make if the application is accepted and funded. Applications for multi-investigator projects should present a management structure for integrating collaborating investigators. Involvement of students and post doctoral scientists is encouraged. For collaborative projects with combined budgets, only one application from the Lead Institution/Lead PI is needed. **However, if the collaborating institution is a DOE Lab, then the DOE Lab portions of the**

budgets (included in the total budgets) will be separately identified with separate budget pages and justifications. If the grant is approved, the DOE Lab portion of funding will be provided directly to the DOE Lab. The Lead Institution to which the grant is funded will not be allowed to charge any indirect expenses for the DOE Lab portion.

Program Funding

It is anticipated that up to $6 million total will be available for multiple awards to be made in FY 2010 for radiochemistry and 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. Applications may request project support for up to three years, with outer-year support contingent on the availability of funds, progress of the research, and programmatic needs. Total annual budgets for single investigator projects are expected to be in the range of $250,000/year. Total annual budgets for multi investigator projects are expected to be in the range of $400,000/year. For budget purposes, applications for a three-year project period, should request 24 months plus 12 months funding (i.e. initial funding for first two years/or 24 months to be provided up front in FY 2010, followed by continuation funding for the third year/or additional 12 months to be provided in FY 2012. When submitting the application a 24 month budget, a 12 month budget and a cumulative budget for 36 months must be included.

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 FOA.

Merit Review

Applications will be subjected to scientific merit review (peer review) and will be evaluated against the following evaluation criteria which are listed in descending order of importance 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; and
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 FOA 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. Both Federal and 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.

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

Posted on the Office of Science Grants and Contracts Web Site
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