

**Program Announcement
To DOE National Laboratories
LAB 09-19**

***Radiochemistry and Radionuclide
Imaging Applications Research***

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. BER hereby announces its interest in receiving peer-reviewable Field Work Proposals (FWPs) to support pilot research projects. These pilot research projects are to develop and study new applications for broader use of transformational new technologies using new radiotracer probes and radionuclide detector devices for dynamic metabolic and molecular imaging of living biological systems. It is anticipated that radiolabeled probes and radionuclide imaging instrumentation already under development by the BER programs will provide transformational new technologies for A) targeting and monitoring a broad variety of important biological processes ranging from enzyme activity to gene expression, B) studying molecular transport across the cellular barriers, inter-cellular communications in microbial communities, and *in situ* metabolism, and C) innovative radiotracer imaging techniques to advance the current state of fundamental science in nuclear medicine. These innovative radiotracers imaging techniques should increase the accuracy of quantitative *in vivo* measurement of site-specific (*in situ*) chemical reactions, and also improve the measurement of any changes in biological processes following various metabolic perturbations. Pilot research projects should focus on transformational technologies that will significantly advance the current state of the science underpinning nuclear medicine research and biological systems research in energy and environmentally relevant contexts.

Program Funding

Total awards in Fiscal Year 2009 are anticipated to be up to \$10,000,000. The number of awards will be contingent on satisfactory peer review, the availability of appropriated funds, and the size of the awards. Individual one time awards for pilot research projects may extend to two-years (FY 2009 and FY 2010). Award requests for projects that extend to two years 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 \$400,000 total costs (direct plus indirect) for one year, and \$800,000 for a two year project period. DOE is under no obligation to pay for any costs associated with the preparation or submission of a research proposal. DOE reserves the right to fund, in whole or in part, any, all, or none of the pilot research projects submitted in response to this LAB Program Announcement.

PREPROPOSALS

Potential proposers are **strongly encouraged** to submit a brief preproposal, referencing LAB Announcement 09-19 for receipt by DOE by 4:30 p.m., Eastern Time, **April 27, 2009**.

Preproposals 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. Preproposals should be sent as a text file without attachments or a single PDF file attachment via e-mail to:

prem.srivastava@science.doe.gov with "LAB Program Announcement 09-19" as the subject. No FAX or mail submission of preproposals will be accepted.

Preproposals will be reviewed for conformance with the guidelines presented in this Program Announcement and suitability in the technical areas specified in this Announcement. A response to the preproposals encouraging or discouraging formal proposals will be communicated to the proposer by **May 1, 2009**. Proposers who have not received a response regarding the status of their preproposal by this date are responsible for contacting the program to confirm this status.

Preproposals 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 preproposal is to save the time and effort of proposers in preparing and submitting a formal proposal that may be inappropriate for the program.

PROPOSAL DUE DATE: May 20, 2009, 8:00 pm, Eastern Time

Full proposals submitted in response to this Program Announcement must be received no later than May 20, 2009, 8:00 p.m., Eastern Time, to be accepted for merit review and to permit timely consideration for award in Fiscal Year 2009-2010.

Please see the "Addresses" section below for further instructions on the method of submission for the proposal.

ADDRESSES:

Please have your lab administrator submit the entire lab proposal and FWP via Searchable FWP (<https://www.osti.gov/fwp>). If you have questions about who your lab administrator is or how to use Searchable FWP, please contact the Searchable FWP Support Center.

Also, to assist in expediting the review process, please submit via federal express, a single PDF file of the entire LAB proposal and FWP on a CD along with two hard copies to the address below.

Please send the CD and 2 hard copies via Federal Express to:

Joanne Corcoran
Biological Systems Science Division, SC-23.2
Office of Biological and Environmental Research

Office of Science
19901 Germantown Road
Germantown, MD 20874-1290
ATTN: Program Announcement LAB 09-19

GENERAL INQUIRIES ABOUT THIS LAB-ANNOUNCEMENT SHOULD BE DIRECTED TO:

Agency Contact:

Dr. Prem C. Srivastava
Phone: (301) 903-4071
Email: prem.srivastava@science.doe.gov

SUPPLEMENTARY INFORMATION:

For over 50 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 our 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 they 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 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 probes. Such target-directed 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 measuring biological processes at the molecular and the metabolic levels. One limitation remains, however, and that relates to the correct spatial and tissue localization of the molecular and metabolic processes so measured. This can be substantially improved with hybrid imaging techniques as has been well demonstrated by PET-Computed Tomography (CT) hybrid imaging. Hence, the development of efficient approaches using dual labeled molecular probes of high specific activity for measuring and accurately localizing biochemical/metabolic process or simultaneously determining two different biochemical or metabolic processes is highly desirable.

Radiolabeled probes (radiotracers) can be detected at concentrations up to 1000-fold lower than those labeled with non-radioactive markers - e.g. magnetic resonance imaging (MRI) contrast agents. 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.

The power of radiotracer imaging for quantitative measurement of biochemical processes and biological function in real-time in living systems (*in vivo*) offers new opportunities to develop synergistic technologies for BER-mission-relevant needs, e.g. probing plants and microbes in energy and environmentally relevant contexts, and for applications to Nuclear Medicine research of interest to the National Institutes of Health (NIH) and industry. For examples, many biological and biochemical processes are relevant and shared across living organisms including animals, plants and microbial communities. Many of the tracers, specialized instruments, and software that have been developed for nuclear medicine medical applications research may be translated to and/or modified for the study of plants, microbial systems, and the environment. Likewise, new chemistry, instrumentation, and data-handling advances made while investigating plant pathways will have relevance to applications in mammalian systems such as diagnostic imaging probes or tools for developing drugs or monitoring therapeutic interventions, thereby advancing nuclear medicine research applications. Broadening the perspective of radiotracer use will drive the technological advances that in turn will benefit a spectrum of biological and nuclear medicine applications.

This LAB Announcement is to request FWPs for one-two year Pilot Research Projects to develop applications of radiochemistry and *in vivo* radionuclide detection methodologies which will be of substantial benefit to BER mission specific needs, and will advance nuclear medicine research through new developments in radiotracer probes and PET or SPECT integrated multi-modality imaging.

General Requirement - Potential Proposals 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 LAB Announcement 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.

Proposals should address hypothesis-driven methodological research to define and/or understand the key physical, chemical, and biological problems influencing the need for the proposed technological advances. Furthermore, these proposals should address the applicability of the proposed research to DOE's stated investments in radiochemistry and imaging instrumentation, and may 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 LAB Announcement 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.

The instructions and format described below must be followed. You must reference Program Announcement LAB 09-19 on all submissions and inquiries about this Program Announcement.

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

After an initial screening for eligibility and responsiveness to the solicitation, proposals will be subjected to scientific merit review (peer review). The proposals will be evaluated against the following criteria, which are listed in descending order of importance. Included with each criteria are the detailed questions that will be asked of the reviewers.

1. Scientific and/or Technical Merit of the Proposed Research
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
5. Other Appropriate Factors

The evaluation process will include program policy factors such as the relevance of the proposed research to the terms of the Announcement and the Department's programmatic needs. 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 a proposal constitutes agreement that this is acceptable to the investigator(s) and the submitting institution.

2. Summary of Proposal Contents

- Field Work Proposal (FWP) Format (Reference DOE Order 412.1A) (DOE ONLY)
- Proposal Cover Page
- Table of Contents
- Budget (DOE Form 4620.1) and Budget Explanation
- Abstract (one page)
- Narrative (main technical portion of the proposal, including background/introduction, proposed research and methods, timetable of activities, and responsibilities of key project personnel)
- Literature Cited
- Biographical Sketch(es)
- Description of Facilities and Resources
- Other Support of Investigator(s)
- Appendix (optional)

2.1 Number of Copies to Submit

Please have your lab administrator submit the entire lab proposal and FWP via Searchable FWP (<https://www.osti.gov/fwp>). If you have questions about who your lab administrator is or how to use Searchable FWP, please contact the Searchable FWP Support Center.

Also, to assist in expediting the review process, please submit via federal express, a single PDF file of the entire LAB proposal and FWP on a CD along with two hard copies to the address below.

Please send the CD and 2 hard copies via Federal Express to:

Joanne Corcoran
Biological Systems Science Division, SC-23.2
Office of Biological and Environmental Research
Office of Science
19901 Germantown Road
Germantown, MD 20874-1290
ATTN: Program Announcement LAB 09-19

3. Detailed Contents of the Proposal

Adherence to type size and line spacing requirements is necessary for several reasons. No researcher should have the advantage, by using small type, of providing more text in their proposals. Small type may also make it difficult for reviewers to read the proposal. Proposals must have 1-inch margins at the top, bottom, and on each side. Type sizes must be at least 11 point. Line spacing is at the discretion of the researcher, but there must be no more than 6 lines

per vertical inch of text. Pages should be standard 8 1/2" x 11" (or metric A4, i.e., 210 mm x 297 mm).

3.1 Field Work Proposal Format (Reference DOE Order 412.1A) (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 Budget and Budget Explanation

A detailed budget is required for the entire project period. 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.science.doe.gov/grants/budgetform.pdf>

3.5 Abstract

Summarize the proposal in no more than two pages. Give the project objectives (in broad scientific terms), the approach to be used, and what the research is intended to accomplish. State the hypotheses to be tested (if any). At the top of the abstract give the project title, names of all the investigators and their institutions, and contact information for the principal investigator, including e-mail address.

3.6 Narrative (main technical portion of the proposal, including background/introduction, proposed research and methods, timetable of activities, and responsibilities of key project personnel).

The narrative comprises the research plan for the project. It should contain enough background material in the Introduction, including review of the relevant literature, to demonstrate sufficient knowledge of the state of the science. The major part of the narrative should be devoted to a description and justification of the proposed project, including details of the methods to be used. It should also include a timeline for the major activities of the proposed project, and should indicate which project personnel will be responsible for which activities. If any portion of the project is to be done in **collaboration** with another institution (or institutions), provide information on the institution(s) and what part(s) of the project it will carry out. 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." Collaborative research projects with institutions that receive grants, such as universities, industry, and non-profit organizations, are allowed under this Announcement. See the section on

Collaboration. Further information on collaboration may be accessed at <http://www.science.doe.gov/grants/Colab.html>.

3.7 Literature Cited

Give full bibliographic entries for each publication cited in the narrative. Each reference must include the names of all authors (in the same sequence in which they appear in the publication), the article and journal title, book title, volume number, page numbers, and year of publication. Include only bibliographic citations. Principal investigators should be especially careful to follow scholarly practices in providing citations for source materials relied upon when preparing any section of the proposal.

3.8 Biographical Sketches

This information is required for senior personnel at the institution submitting the proposal and at all subcontracting institutions (if any). The biographical sketch is limited to a maximum of two pages for each investigator and must include:

Education and Training. Undergraduate, graduate and postdoctoral training, provide institution, major/area, degree and year.

Research and Professional Experience. Beginning with the current position list, in chronological order, professional/academic positions with a brief description.

Publications. Provide a list of up to 10 publications most closely related to the proposed project. For each publication, identify the names of all authors (in the same sequence in which they appear in the publication), the article title, book or journal title, volume number, page numbers, year of publication, and website address if available electronically. Patents, copyrights and software systems developed may be provided in addition to or substituted for publications.

Synergistic Activities. List no more than 5 professional and scholarly activities related to the effort proposed.

To assist in the identification of potential conflicts of interest or bias in the selection of reviewers, the following information must also be provided in each biographical sketch.

Collaborators and Co-editors: A list of all persons in alphabetical order (including their current organizational affiliations) who are currently, or who have been, collaborators or co-authors with the investigator on a research project, book or book article, report, abstract, or paper during the 48 months preceding the submission of the proposal. Also, include those individuals who are currently or have been co-editors of a special issue of a journal, compendium, or conference proceedings during the 24 months preceding the submission of the proposal. If there are no collaborators or co-editors to report, this should be so indicated.

Graduate and Postdoctoral Advisors and Advisees: A list of the names of the individual's own graduate advisor(s) and principal postdoctoral sponsor(s), and their current organizational affiliations. A list of the names of the individual's graduate students and postdoctoral associates during the past five years, and their current organizational affiliations.

3.9 Description of Facilities and Resources

Facilities to be used for the conduct of the proposed research should be briefly described. Indicate the pertinent capabilities of the institution, 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).

3.10 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 (months per year or percentage of the year) devoted to the project.

3.11 Appendix

Information not easily accessible to a reviewer may be included in an appendix, but do not use the appendix to circumvent the page limitations of the proposal. Reviewers are not required to consider information in an appendix, and reviewers may not have time to read extensive appendix materials with the same care they would use with 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 \$50,000 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.