Office of Science
Notice 00-02

Experimental and Computational Structural Biology

Department of Energy
Office of Science

Office of Science Financial Assistance Program Notice 00-02; Experimental and Computational Structural Biology

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 in its Experimental and Computational Structural Biology Program. Research is sought for experimental and computational biological studies on the structural biology of proteins involved in DNA repair or in bioremediation.

DATES: Before preparing a formal application, potential applicants are encouraged to submit a brief preapplication. All preapplications, referencing Program Notice 00-02, should be received by DOE by 4:30 P.M., E.S.T., January 12, 2000. A response encouraging or discouraging the submission of a formal application will be communicated by electronic mail by January 25, 2000.

Formal applications submitted in response to this notice must be received by 4:30 P.M., E.D.T., May 2, 2000, to be accepted for merit review and consideration for award in Fiscal Years 2000 and 2001.

ADDRESSES: Preapplications referencing Program Notice 00-02, 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, Maryland 20874-1290.

Formal applications, referencing Program Notice 00-02, should be forwarded to: U.S. Department of Energy, Office of Science, Grants and Contracts Division, SC-64, 19901 Germantown Road, Germantown, Maryland 20874-1290, ATTN: Program

Notice 00-02. 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. Roland F. Hirsch, Office of Biological and Environmental Research, SC-73, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290, telephone: (301) 903-9009, FAX: (301) 903-0567, E-mail: roland.hirsch@science.doe.gov. Concerning the DNA Damage Recognition and Repair aspects: Dr. David G. Thomassen, Office of Biological and Environmental Research, SC-72, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290, telephone: (301) 903-9817, FAX: (301) 903-8521, E-mail: david.thomassen@science.doe.gov. Concerning the Bioremediation aspects: Dr. Anna C. Palmisano, Office of Biological and Environmental Research, SC-73, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290, telephone: (301) 903-9963, FAX: (301) 903-8519, E-mail: anna.palmisano@science.doe.gov. The full text of Program Notice 00-02 is available via the Internet using the following web site address: http://www.sc.doe.gov/production/grants/grants.html.

SUPPLEMENTARY INFORMATION: The Office of Biological and Environmental Research supports a directed, basic research program in the areas of environmental, life and medical science. Major research program emphases are placed on characterization of human and microbial genomes, model organisms for understanding human gene function, structural biology, the biological effects of low dose radiation, global change, science and technology for environmental remediation, advanced imaging technologies, biomedical engineering and molecular nuclear medicine.

Nucleic acid and derived amino acid sequence data are flowing from genome projects at an accelerating rate. Utilizing the genomic sequence as a blueprint, large-scale high-throughput three-dimensional structural analysis of cell proteins is planned. However, knowledge of high resolution protein structure will not be sufficient for understanding of protein function in the cellular environment. Proteins do not act independently or statically in living systems. In carrying out their functions within cells, proteins form complexes with other proteins and interact with a variety of structural, regulatory and ligand molecules. The role of structure in determining protein interactions with diverse molecules in a cell is still poorly understood. It is necessary to observe dynamic changes in protein structure and to study protein modifications, translocation, and subcellular concentrations to fully understand protein function. Such studies are therefore a major focus of this program.

The transformation of the accumulating database of genomic information into a practical understanding of structure-function relationships in biological macromolecules and of the complicated systems that constitute living cells, tissues and organisms is paramount. The ultimate goal is to extend the understanding of the function and behavior of individual proteins to the genome scale through escalating levels of complexity from functional aggregates to metabolic circuits and homeostatic networks. This approach will eventually lead to a systems view of biology. This will enable diverse applications in human health, including individualized medicine and drug design, in biotechnology, including, new and improved biomaterials and new biocatalysis in industry and manufacturing, in environmental science for the design of enzymes for effective and efficient removal of environmental contaminants and in energy technology for the development and conversion of biomass for fuels.

This notice is to solicit applications for grants for experimental and computational structural biology studies to expand our understanding of the function of proteins and protein complexes relevant to two high priority research programs within the Office of Biological and Environmental Research: 1) Recognition and repair of DNA damage, and 2) Bioremediation of environmental contamination by metals and radionuclides.

DNA Damage Recognition and Repair

The Office of Biological and Environmental Research has a long standing interest in determining health risks from exposures to low levels of radiation, information that is critical to adequately and appropriately protect people and to make the most effective use of our national resources. The Low Dose Radiation Research Program (see http://www.sc.doe.gov/production/ober/lowdose.html), supports research on the recognition and repair of DNA damage induced by low doses of ionizing radiation. Understanding cellular DNA damage recognition and repair in response to low doses of radiation is a key component of determining health risks from low doses of radiation and is likely to be a significant factor in identifying genetic factors that determine individual sensitivity to low doses of radiation.

The Office of Biological and Environmental Research will accept applications to study proteins involved in the recognition and repair of radiation-induced DNA damage in prokaryotes and eukaryotes (including humans). Studies of interest include the following:

- High-resolution three-dimensional structure of normal and mutated DNA damage recognition and repair proteins using X-ray crystallography and NMR with an emphasis on structure/function relationships.

- Dynamic changes in protein structure associated with protein modification and with protein-protein and protein-DNA interactions that occur during the recognition and repair of radiation-induced DNA damage.
- Imaging of multi-protein DNA damage recognition and repair complexes, including high resolution, real-time optical imaging.
- Precise measurements of DNA damage recognition and repair protein concentrations, intracellular compartmentalization, and translocations in response to ionizing radiation.

Bioremediation

The Office of Biological and Environmental Research supports bioremediation research in its Natural and Accelerated Bioremediation Research Program (NABIR) (see http://www.sc.doe.gov/production/ober/EPR/nabir.html and http://www.lbl.gov/NABIR/). The major focus of this program is to gain a better understanding of the fundamental biological, chemical, geological, and physical processes that must be marshaled for the development and advancement of new, effective, and efficient processes for the remediation and restoration of the Nation's nuclear weapons production sites. A particular goal is to use molecular and structural biology to enable understanding of potential microbial remediation processes and to genetically modify macromolecules and organisms to improve their bioremedial activities. Many molecules, enzymes, and enzyme pathways that may be effective for bioremediation of metals and radionuclides are being identified.

The Office of Biological and Environmental Research will accept applications for structural biological studies in the area of bioremediation, particularly those concerned with the reduction of metals and radionuclides in microbes (e.g., Shewanella putrefaciens MR 1). Studies of interest include the following:

- High resolution three dimensional structure of proteins involved in critical functions of microorganisms relevant to bioremediation processes, particularly those proteins involved in reducing metals and radionuclides. Structure/function relationships should be stressed.
- Dynamic changes in protein structure related to the binding and reduction of metals and radionuclides.
- Realtime visualization of protein complexes involved in these bioremediation functions.
- Studies, comparable to those outlined above, on genetically modified proteins and protein complexes with potential to contribute to the bioremediation of metals and radionuclides.

Computational Structural Biology

The Office of Biological and Environmental Research is interested in the development of improved computational approaches for finding the proteins involved in DNA repair or in bioremediation processes, for predicting the three dimensional structures of these proteins, or for modeling the complex interactions of these proteins in living organisms. Computational approaches to predict protein structure and function will play an increasingly important role as the complete genomic sequences of more organisms, including human, are made available over the next few years. These computational approaches will also provide an important interface with the projected increases in the rate of protein structure determination. This program is focusing on sophisticated prediction, modeling, and simulation research to provide a generalizable approach to the interrelationship of macromolecular sequence, structure, and function with specific applications in DNA repair or in bioremediation.

The program places emphasis on projects that advance or integrate existing software tools in novel ways and/or develop new computational strategies to exploit databases of macromolecular structural information, including both high and low resolution. This includes the goal of predicting the structure and function of newly discovered gene sequences as well as the prediction or computational design of the chemical properties and architectural arrangement of proteins, protein-protein complexes, or protein-nucleic acid complexes needed for a particular functional application.

The Office of Biological and Environmental Research will accept applications for the development and use of computational tools that would ultimately accomplish one or more of the following objectives. A clear path should be presented from the fundamental computational research to be carried out to the testing of the new algorithms on one or more of these objectives:

- Develop high throughput computational methods to predict or identify, from sequence information, proteins involved in the recognition or repair of radiation- induced DNA damage or in the bioremediation of metals and radionuclides. This predictive capability will be essential for understanding the complete structure, function, and dynamic behavior of multiprotein complexes.
- Predict from sequence the structure or the function of proteins involved in the recognition or repair of radiation-induced DNA damage or in the bioremediation of metals and radionuclides.
- Characterize or simulate molecular interactions between proteins, proteins and DNA, or proteins and ligand molecules involved in the recognition or repair of radiation- induced DNA damage or in the bioremediation or metals and radionuclides including changes due to genetically modified proteins.

Program Funding

It is anticipated that up to $3 million will be available for multiple grant awards during Fiscal Years 2000 and 2001 contingent upon the availability of appropriated funds. 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. We expect to award several research grants of up to $300,000 per year in this area.

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, and the research element(s) being addressed (DNA Damage Recognition and Repair; Bioremediation; or Computational Structural Biology). The preapplication should consist of two to three pages identifying and describing the research objectives, methods for accomplishment, and potential benefits of the effort. Preapplications will be evaluated relative to the scope and research needs for the Experimental and Computational Structural Biology Program.

Applications

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.

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. 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

Published in the Federal Register November 10, 1999, Volume 64, Number 217, Pages 61318-61321.