Program Announcement To DOE National Laboratories
LAB 00-02
Experimental and Computational Structural Biology

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 proposals in its Experimental and Computational Structural Biology Program. Integrated, multidisciplinary research projects are sought for experimental and computational biological studies on the structural biology of proteins involved in DNA repair or in bioremediation.

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 announcement is to solicit Proposals for highly integrated, multidisciplinary experimental and computational structural biology projects 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. Proposals that address one or more of the issues defined in the following paragraphs through collaborations among scientists in two or more disciplines and through leveraging of unique laboratory facilities and resources are strongly encouraged. Collaborations with scientists at other institutions are also encouraged where appropriate.

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 proposals 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 proposals 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 proposals 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.

DATES: Before preparing a formal proposal, potential proposers are encouraged to submit a brief preproposal. All preproposals, referencing Program Announcement LAB00-02, should be received by DOE by 4:30 P.M., EST, January 12, 2000. A response encouraging or discouraging the submission of a formal proposal will be communicated by electronic mail on January 25, 2000.

Formal proposals submitted in response to this announcement must be received by 4:30 P.M., EST, May 2, 2000, to be accepted for merit review and consideration for award in Fiscal Years 2000 and 2001.

ADDRESSES: Preproposals referencing Program Announcement LAB00-02, must be sent by E-mail to sharon.betson@science.doe.gov. Preproposals 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 proposals, referencing Program Announcement LAB00-02, should be forwarded to: U.S. Department of Energy, Office of Science, Office of Biological and Environmental Research, SC-73, 19901 Germantown Road, Germantown, Maryland 20874-1290, ATTN: Program Announcement LAB00-02. This address must also be used when submitting proposals 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 proposal 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.

Program Funding

It is anticipated that up to $5.0 million will be available for awards during Fiscal Years 2000 and 2001 contingent upon the availability of appropriated funds. Proposals 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.

Preproposals

A brief preproposal should be submitted. The preproposal 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 preproposal should consist of two to three pages identifying and describing the research objectives, methods for accomplishment, and potential benefits of the effort. Preproposals will be evaluated relative to the scope and research needs for the Experimental and Computational Structural Biology Program.

Any recipient of an award from SC 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 instructions and format described below should be followed. Reference Program Announcement LAB00-02 on all submissions and inquiries about this program.

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

Proposals will be subjected to formal merit review (peer review) and will be evaluated against the following criteria which are listed in descending order of importance:

Scientific and/or technical merit of the project

Appropriateness of the proposed method or approach

Competency of the personnel and adequacy of the proposed resources

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, the uniqueness of the proposer's capabilities, and demonstrated usefulness of the research for proposals in other DOE Program Offices as evidenced by a history of programmatic support directly related to the proposed work.

2. Summary of Proposal Contents

Field Work Proposal (FWP) Format (Reference DOE Order 5700.7C) (DOE ONLY)
Proposal Cover Page
Table of Contents
Abstract
Narrative
Literature Cited
Budget and Budget Explanation
Other support of investigators
Biographical Sketches
Description of facilities and resources
Appendix

2.1 Number of Copies to Submit

An original and seven copies of the formal proposal/FWP must be submitted.

3. Detailed Contents of the Proposal

Proposals must be readily legible, when photocopied, and must conform to the following three requirements: the height of the letters must be no smaller than 10 point with at least 2 points of spacing between lines (leading); the type density must average no more than 17 characters per inch; the margins must be at least one-half inch on all sides. Figures, charts, tables, figure legends, etc., may include type smaller than these requirements so long as they are still fully legible.

3.1 Field Work Proposal Format (Reference DOE Order 5700.7C)
(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 Abstract

Provide an abstract of no more than 250 words. Give the broad, long-term objectives and what the specific research proposed is intended to accomplish. State the hypotheses to be tested. Indicate how the proposed research addresses the SC scientific/technical area specifically described in this announcement.

3.5 Narrative

The narrative comprises the research plan for the project and is limited to 25 pages. It should contain the following subsections:

Background and Significance: Briefly sketch the background leading to the present proposal, critically evaluate existing knowledge, and specifically identify the gaps which the project is intended to fill. State concisely the importance of the research described in the proposal. Explain the relevance of the project to the research needs identified by the Office of Science. Include references to relevant published literature, both to work of the investigators and to work done by other researchers.

Preliminary Studies: Use this section to provide an account of any preliminary studies that may be pertinent to the proposal. Include any other information that will help to establish the experience and competence of the investigators to pursue the proposed project. References to appropriate publications and manuscripts submitted or accepted for publication may be included.

Research Design and Methods: Describe the research design and the procedures to be used to accomplish the specific aims of the project. Describe new techniques and methodologies and explain the advantages over existing techniques and methodologies. As part of this section, provide a tentative sequence or timetable for the project.

Subcontract or Consortium Arrangements: If any portion of the project described under "Research Design and Methods" is to be done in collaboration with another institution, provide information on the institution and why it is to do the specific component of the project. 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".

3.6 Literature Cited

List all references cited in the narrative. Limit citations to current literature relevant to the proposed research. Information about each reference should be sufficient for it to be located by a reviewer of the proposal.

3.7 Budget and Budget Explanation

A detailed budget is required for the entire project period, which normally will be three years, and for each fiscal year. 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.sc.doe.gov/production/grants/forms.html

3.8 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 devoted to the project.

3.9 Biographical Sketches

This information is required for senior personnel at the laboratory submitting the proposal and at all subcontracting institutions. The biographical sketch is limited to a maximum of two pages for each investigator.

3.10 Description of Facilities and Resources

Describe briefly the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe pertinent capabilities, 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.

3.11 Appendix

Include collated sets of all appendix materials with each copy of the proposal. Do not use the appendix to circumvent the page limitations of the proposal. Information should be included that may not be easily accessible to a reviewer.

Reviewers are not required to consider information in the Appendix, only that in the body of the proposal. Reviewers may not have time to read extensive appendix materials with the same care as they will read 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 $5000 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.