Office of Science
Notice 99-19

Computational Structural Biology

.....CANCELLED Aug. 10, 1999.....

Department of Energy
Office of Science

Office of Science Financial Assistance Program Notice 99-19; 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 Computational Structural Biology subprogram. There is an immediate need for greatly improved computational approaches for gene product structure and function elucidation. This solicitation seeks sophisticated prediction, modeling and simulation research for the exploration of the interrelationship of macromolecular sequence, structure and function. The goal will be to establish a robust computational process for predicting the three-dimensional architecture for gene products and for gaining further insight into their biological role.

DATES: Before preparing a formal application, potential applicants are encouraged to submit a brief preapplication. All preapplications, referencing Program Notice 99-19, should be received by DOE by 4:30 P.M., E.D.T., June 15, 1999. A response discussing the programmatic relevance of the proposed submission will be communicated by July 1, 1999.

Formal applications submitted in response to this notice must be received by 4:30 P.M., E.D.T., October 5, 1999, to be accepted for merit review and consideration for award in mid-Fiscal Year 2000.

ADDRESSES: Preapplications referencing Program Notice 99-19, 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 99-19, 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 99-19. 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. Charles G. Edmonds, Office of Biological and Environmental Research, SC-73, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290, telephone: (301) 903-0042, FAX: (301) 903-0567, E-mail: charles.edmonds@science.doe.gov. The full text of Program Notice 99-19 is available via the Internet using the following web site address: http://www.er.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 climate change, improved technology for cleanup of DOE contaminated sites, advanced imaging technologies, and molecular nuclear medicine. With the accelerating increase in nucleic acid and derived amino acid sequence data flowing from genome projects and in the particular context of these DOE supported basic research efforts, there is an immediate need for greatly improved experimental and computational approaches for gene product structure and function determination. OBER presently supports a program in computational structural biology that is intended to address this need.

This notice is to solicit applications for grants to maintain and enhance this program which focuses on sophisticated prediction, modeling and simulation research to provide a generalizable approach to the interrelationship of macromolecular sequence, structure and function. The rapid influx of newly discovered genes, the remarkably large proportion of which no function can so far be inferred, require a global predictive capability. We are seeking tools for the robust prediction of structure and inference of function for any gene and on a whole genome scale of analysis.

Research applications that 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 structures, are a continuing interest of the program. This includes the goals 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 or nucleic acids needed for a particular functional application. Examples of existing approaches that fall into this category are knowledge-based or molecular extension methods (e.g., homology model building), ab initio structure prediction (finding structures that fit sequences) and the development of tools to assign existing or new sequences to specific structures (e.g., finding sequences that fit structures through threading or inverse folding algorithms). Attention may also be focussed on the problem of negative design, the identification of aspects of sequence that precludes its fitting a known structure. Awardees will be expected to attend the biannual Critical Assessment of Techniques for Protein Structure Prediction (CASP) experiment and participate at an appropriate level in the comparative exercise.

Further, the use of structure from experimental and/or computational sources to provide insight into function is a specific target of this solicitation. Computational and visualization techniques exploiting structure to characterize recognition within macromolecular ensembles, ligand-receptor and other specific molecular interactions and to extend this to the understanding and modeling of elaborate functional aggregates including metabolic pathways and interacting circuits are specifically encouraged. This solicitation includes but is not limited to participation in structural genomics projects, i.e., the collaborative experimental, theoretical and computational efforts which seek to establish a catalogue of the structures of a representative set of protein folds occurring in nature and thus facilitating the modeling of the structure of any genomically derived amino acid sequence by reference to its nearest catalogued archetype.

Applications that exploit the latest multiple approaches (in algorithms, simulation, modeling and graphical representation/visualization) or provide for the interpretation and the integration and joint utilization through the World Wide Web of the growing body of sequence, structural and physical information tools will also be considered particularly responsive. We encourage the development of teams to accelerate the deployment of robust software available to the entire community. Established programs should demonstrate such capabilities or discuss plans for web access and dissemination. The long term goal of the program is to develop well-integrated software packages that meet the scientific and technical goals outlined above.

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 which constitute living cells, tissues and organisms is paramount. The ultimate objective of the extension of this new

understanding of individual reactive entities to the genome scale will be the elucidation of a vocabulary and grammar of connectedness in molecular function. Through escalating levels of complexity from functional aggregates to metabolic circuits and homeostatic networks we will arrive at 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.

Program Funding

It is anticipated that approximately $2.0 million will be available for multiple grant awards during Fiscal Year 2000 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 grants in this area of research of up to $500,000 per year.

Preapplications

A brief preapplication should be submitted. The preapplication should identify on the cover sheet the institution, PI name, address, telephone, fax and E-mail address for the principal investigator, and title of the project. The preapplication should consist of two to three pages narrating the research objective, methods for accomplishment and benefits of the effort.

Preapplications will be evaluated relative to the scope and research needs for the Computational Structural Biology subprogram.

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 an 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.

To provide a consistent format for the submission, review and solicitation of grant applications submitted under this notice, the preparation and submission of grant applications must follow the guidelines given in the Application Guide for the Office of Science Financial Assistance Program 10 CFR Part 605.

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.er.doe.gov/production/grants/grants.html. 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.

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

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