

Office of Science
Notice 01-20

Microbial Cell Project

Department of Energy
Office of Science

Office of Science Financial Assistance Program Notice 01-20; Microbial Cell Project

AGENCY: U. S. Department of Energy (DOE)

ACTION: Notice inviting grant applications

SUMMARY: The Offices of Biological and Environmental Research (OBER), Basic Energy Sciences (BES), and Advanced Scientific Computing Research (ASCR) of the Office of Science (SC), U.S. Department of Energy, hereby announce their interest in receiving applications for research grants in support of the Microbial Cell Project (MCP), an effort to build on information from completely sequenced microbial genomes to achieve a more comprehensive understanding of the functioning of a prokaryotic microbial cell. This notice encourages applications from interdisciplinary scientific partnerships or teams that include such disciplines as microbiology, molecular biology, applied mathematics, biochemistry, structural and computational biology, as well as physics, chemistry, engineering and computer science. The MCP is focused on fundamental research to understand those reactions, pathways, and regulatory networks that are involved in environmental processes of relevance to the DOE, specifically the bioremediation of metals and radionuclides, cellulose degradation, carbon sequestration, and the production, conversion, or conservation of energy (e.g. fuels, chemicals, and chemical feedstocks). Research areas of particular interest that should be integrated into an interdisciplinary approach can include studies of: 1) functional analysis of the microbial proteome; 2) biochemical and physiological characterization; 3) intracellular localization; and 4) cell modeling. This announcement represents a planned first step in an ambitious effort to understand the functions of all the macromolecular components in a microbial cell, to understand all their interactions as they form pathways and processes that are related to DOE-relevant activities, and to eventually build predictive models for microbial activities that address DOE mission needs.

DATES: Preapplications referencing Program Notice 01-20 should be received by February 21, 2001. Earlier submissions will be gladly accepted. A response to timely preapplications will be communicated to the applicant by March 9, 2001.

Formal applications in response to this notice should be received by 4:30 p.m., E.D.T., April 24, 2001, to be accepted for merit review and funding in FY 2001.

ADDRESSES: Preapplications referencing Program Notice 01-20 should be sent to Dr. Daniel W. Drell, Office of Biological and Environmental Research, SC-72, Office of Science, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290; e-mail is encouraged (but not required) for submitting preapplications using the following address: joanne.corcoran@science.doe.gov.

Formal applications referencing Program Notice 01-20, should be forwarded to: U.S. Department of Energy, Office of Science, Grants and Contracts Division, SC-64, 19901 Germantown Road, Germantown, MD 20874-1290, ATTN: Program Notice 01-20. This address must be used when submitting applications by U.S. Postal Service Express Mail or any commercial mail delivery service, or when hand-carried by the applicant.

FOR FURTHER INFORMATION CONTACT:

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The full text of Program Notice 01-20 is available via the World Wide Web using the following web site address: <http://www.sc.doe.gov/production/grants/grants.html>.

SUPPLEMENTARY INFORMATION: The Microbial Cell Project (MCP) supports key DOE missions by building on the successful DOE Microbial Genome Program that has furnished microbial DNA sequence information on microbes relevant to environmental remediation, global carbon sequestration (e.g. CO₂ fixation), complex polymer degradation (e.g. cellulose and lignins), and energy production (fuels, chemicals, and chemical feedstocks). These microbial genome sequences provide a finite set of “working parts” for a cell; the challenge now is to understand how these parts are assembled into functional pathways and networks to accomplish activities of interest to the DOE (specifically those identified in the preceding sentence.) The traditional reductionist experimental approach has defined specific steps or stages within many physiological processes; however, the availability of whole genomes affords the opportunity to integrate these individual pathways into a larger physiological or whole organism framework. The MCP seeks to integrate available information about individual processes and regulatory complexes to understand the intracellular environment in which these pathways and networks exist and function. The DOE Microbial Cell Project is part of a coordinated Federal effort called the Microbe Project involving elements from several other Federal agencies.

This notice strongly encourages interdisciplinary teams that assemble a range of expertise into an integrated approach to characterizing the structure and function of a prokaryotic cell. The purpose of encouraging interdisciplinary teams is to combine diverse scientific talents into a coordinated program and thus it is very important that a coordination plan describing how the whole exceeds the sum of the parts be included in the application. In addition, the MCP seeks to promote research on the internal organization and complex control systems that allow microbial cells to respond to their environment, to make unique products, and to carry out specialized functions relevant to DOE missions in the bioremediation of metals and radionuclides, cellulose degradation, carbon sequestration, and the production, conversion, or conservation of energy. This effort will exploit a range of approaches, among them: 1) functional analyses of proteins and protein interactions; 2) metabolic and flux measurements; 3) intracellular imaging technologies for the localization and quantitation of proteins and other cellular constituents; and 4) computational modeling to represent the activities of a cell in ways that permit testable predictions of microbial cell functions.

Preference will be given to those applications selecting prokaryotic microbes that satisfy all of the following criteria: a) the chosen microbe is of DOE mission-relevance, i.e., can bioremediate metals and radionuclides, sequesters environmental carbon, e.g., can fix CO₂, degrades significant biopolymers such as celluloses and

lignins, or generates energy sources, fuels, chemicals, and chemical feedstocks. Strict pathogens or parasites will not be considered; b) complete or near-complete genomic sequencing information from the chosen microbe exists in the public domain; c) the chosen microbe grows sufficiently in culture to enable experimental work; d) the chosen microbe can easily be genetically transformed; and e) expression vectors are available. Of particular importance will be a clear description of a coherent plan for making efficient use of the available sequence information. (See <http://www.ornl.gov/microbialgenomes/organisms.html> for a current list of microbes that have been and are being sequenced.) If a group proposes to carry out work under this notice on a specific microbe, it should be prepared to justify the merits of the chosen target organism to the peer review process. It is expected that each project supported by the MCP will be focused on an energy-related or environmentally relevant microbe (or group of microbes) for which extensive sequence information is known, although applicants may take advantage of relevant information derived from other microbes that are not considered DOE targets, e.g. *E. coli* or yeast. While integrated and multidisciplinary consortia are strongly encouraged, exceptional applications from individual investigators focused on more confined aspects or areas may be considered.

This program notice encourages research applications that integrate the following highly interrelated thrusts, using a single, sequenced, DOE-relevant microbe as the unifying cornerstone. For the purposes of this notice, the interests of DOE are the bioremediation of metals and radionuclides, cellulose degradation, carbon sequestration, and energy production, conversion, or conservation. Integrated applications should include a careful description of how the project's proposed interdisciplinary research team will integrate all or most of the following components into a single research project. These components are:

1) Functional Analysis of the Microbial Proteome. It is presently difficult, and in many instances impossible, to predict biological function from microbial genomic sequence data, even when the entire genome has been sequenced and is available for inspection. Applications should discuss better ways to exploit sequence data from novel open reading frames, and even whole genomes, to characterize the pathways and networks that mediate microbial physiology and function, and how they are regulated under different environmental conditions. This effort can take place at different levels of resolution: a medium-resolution (less detailed) analysis of novel or unannotated genes and open reading frames across an entire sequenced microbial genome or a higher-resolution (more comprehensive) analysis of novel or unannotated genes and open reading frames that participate in one or a few processes supporting the stated interests of DOE. The research emphasis should be on whole genome approaches to

functional prediction, functional regulation, functional categorization (at medium resolution), or on specific systems, e.g., redox enzymes, metal reductases, or hydrogen or methane production components (at high resolution). Applications may include the use of new high-throughput technologies/tools to better understand expression patterns and protein profiles, as well as the exploitation of functional manipulations to better understand pathways relevant to the DOE. Identification of domains in gene sequences that mediate protein-protein interactions that are part of these kinds of pathways are also of great interest. An explicit intention of this notice is to promote research on DOE mission relevant protein complexes, pathways, and processes and their biochemistry, physiology and regulation as a basis for understanding function. Studies on individual proteins are not encouraged.

2) Biochemical and Physiological Characterization. The MCP seeks to go beyond identifying discrete genes and proteins that participate in a few isolated enzymatic reactions; the interest is in defining the global interactions among multiple cellular components. How do these proteins, metabolites, or cellular biomolecules interact with each other to form functional networks or linkages between the constituents of traditionally described modular pathways? There is an acute need to know more about the quantitative intracellular physiology and biochemistry of a microbial cell's constituents, e.g., assembly dynamics, kinetics, and fluxes of relevant proteins and cytoplasmic components under *in vivo* conditions. Applications may include the use of new high-throughput technologies/tools to better quantify protein biochemistry inside a cell in response to different conditions and to better understand regulatory molecules and noncoding regulatory sequences that affect pathways relevant to the DOE. Of particular interest, are explorations of the physical mechanisms of intracellular communication and information exchange that underlie the DOE mission relevant processes listed earlier in this notice. This notice does not encourage research applications directed toward microarray or "gene-chip" development or construction; however, such arrays or chips may be used to address the aims of this notice.

3) Intracellular Localization. A microbial cell is not a simple "bag of dilute saline" in which proteins freely diffuse and interact in ways solely governed by simple diffusion. Although this assumption (of simplicity) has proven useful in studying protein biochemistry and reaction kinetics at the level of single enzymes, it does not represent the internal reality of even a simple microbial cell. This notice encourages research on the intracellular physico-chemical environment, including the intracellular distribution, localization, movement, temporal variations, and topological or mechanical constraints on physiological

function of microbial proteins involved in reaction pathways and networks that are of interest to DOE. Technologies for imaging microbial cell constituents in real time are also of interest.

4) Cell Modeling. It is not presently possible to model every single interaction in a cell, much less represent its overlapping but distinct networks and pathways in sufficient detail to capture most its complexity. This notice encourages research applications to develop and explore computational models of those networks and pathways of interest to the DOE. Computational models are sought to simulate the intracellular environment at different levels of resolution: a) at medium resolution, i.e., modeling most of a cell's proteome, to generate a rough or approximate predictive understanding of the "minimal metabolic scaffold" for processes such as methanogenesis, photosynthesis, or metal reduction, or b) at higher resolution: i.e. for a detailed quantitative representation of a relevant physiological process to optimize or manipulate a particular reaction, and to accurately predict responses to environmental perturbations. It is important that any proposed software development activities be based on modular design, which enables upgrades and expansions to the predictive modeling capability as more quantitative data about protein biochemistry, physiology, and intracellular topology becomes available. Of particular importance is that modeling efforts not be conducted in isolation from the biological "reality" derived from experimental research. Of special interest will be computational models that would effectively utilize investments made by the Office of Science in massively parallel, high- performance computing hardware and software libraries. It is expected that computational tools developed under these awards will be widely distributed to the scientific community (e.g. via a WWW site) and that some level of user support will be available. Applicants with an interest in this thrust area are strongly encouraged to explore the companion Program Notice 01-21, *Advanced Modeling and Simulation of Biological Systems*, which encourages the submission of research applications that emphasize the applied mathematics and computer science advances needed to provide the computational modeling foundation upon which this notice is focused.

Preapplications

Potential applicants are strongly encouraged to submit a brief preapplication that consists of two to three pages of narrative describing the research objectives, the technical approach(s), and the proposed team members and their expertise. 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. Preapplications will be reviewed relative to the scope and research needs of the

Microbial Cell Project, as outlined in the summary paragraph and in the SUPPLEMENTARY INFORMATION. The preapplication should identify, on the cover sheet, the title of the project, the institution, principal investigator name, telephone, fax, and e-mail address. No budget information or biographical data need be included, nor is an institutional endorsement necessary. A response to timely preapplications will be communicated to the Principal Investigator by March 9, 2001.

Program Funding

It is anticipated that up to \$6 million will be available for all MCP awards in Fiscal Year 2001. It is anticipated that at least 4 awards will be made to interdisciplinary scientific teams, contingent on satisfactory peer review, the availability of funds, and the size of the awards. Multiple year funding is expected, also contingent on availability of funds and progress of the research; pending the availability of future funding, it is anticipated that this initiative will reflect a long term commitment to understanding the workings of a microbial cell. Awards to interdisciplinary teams are expected to range from \$0.5 million to \$1.5 million per year, total costs, with terms of one to three years. (A number of awards in the \$100 – 200 thousand range, total annual costs, may be made to exceptional individual investigator applications). The 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 Notice. Applications received by the Office of Science under its normal competitive application mechanisms may also be deemed appropriate for consideration under this announcement and may be funded under this program.

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;
4. Reasonableness and Appropriateness of the Proposed Budget.

In addition to the above evaluation criteria, applications will also be evaluated on the following:

5. The robustness of the organizational framework and its coordination plan if a consortium is proposed.

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 will often be used, and submission of an application constitutes agreement that this is acceptable to the investigator(s) and the submitting institution.

Submission Information

The Project Description must be 25 pages or less, exclusive of attachments. It must contain an abstract or project summary on a separate page with the name of the applicant, mailing address, phone FAX and E-mail listed. The application must include letters of intent from collaborators (briefly describing the intended contribution of each to the research), and short curriculum vitae, consistent with NIH guidelines, for the applicant and any co-PIs.

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. Access to SC's Financial Assistance Application Guide is possible via the World Wide Web at:

<http://www.sc.doe.gov/production/grants/grants.html>.

DOE policy requires that potential applicants adhere to 10 CFR Part 745 "Protection of Human Subjects" (if applicable), 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 (10 CFR 605.11(b)) requires that a grantee funded by SC and performing research involving recombinant DNA molecules and/or organisms and viruses containing recombinant DNA molecules shall comply with the 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.

Other useful web sites include:

MCP Home Page – <http://microbialcellproject.org>

Microbial Genome Program Home Page -
<http://www.er.doe.gov/production/ober/microbial.html>

DOE Joint Genome Institute Microbial Web Page -
http://www.jgi.doe.gov/JGI_microbial/html/

GenBank Home Page - <http://www.ncbi.nlm.nih.gov/>

Human Genome Home Page - <http://www.ornl.gov/hgmis>

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

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for Resource Management

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