Office of Science
Notice 00-18

Microbial Genome Program

Department of Energy
Office of Science

Office of Science Financial Assistance Program Notice 00-18; Microbial Genome Program

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 applications for grants in support of the Microbial Genome Program (MGP), focused on microbes of interest to the DOE, e.g. those involved in environmental processes, including waste remediation, carbon management, energy production and biotechnology. This announcement is focused on 1) whole genome functional analyses of genomic information from microorganisms; 2) bioinformatics tools for microbial genome annotation; 3) characterization of microbial genomic plasticity, e.g. lateral gene transfers and other forms of genomic information transfer; 4) novel technologies for comparative microbial genome sequencing that exploit previously sequenced microbial genomes; and 5) technologies to assess consortia and environmental diversity of hard-to-culture microbes. This announcement represents a significant departure from past MGP announcements in that the DOE will not solicit applications to continue high throughput sequencing of microbial genomes. Rather, this is a shift in emphasis to exploiting already sequenced genomes to address DOE mission needs.

DATES: Preapplications referencing Program Notice 00-18 should be received by October 2, 2000.

Formal applications in response to this notice should be received by 4:30 p.m., E.S.T., December 14, 2000, to be accepted for merit review and funding in FY 2001.

ADDRESSES: Preapplications referencing Program Notice 00-18 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 acceptable for submitting preapplications using the following address: joanne.corcoran@science.doe.gov.

Formal applications referencing Program Notice 00-18, 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 00-18. 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: Dr. Daniel W. Drell, SC-72, Office of Biological and Environmental Research, Office of Science, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290, telephone: (301) 903-4742, e-mail: daniel.drell@science.doe.gov. The full text of Program Notice 00-18 is available via the Internet using the following web site address: http://www.sc.doe.gov/production/grants/grants.html.

SUPPLEMENTARY INFORMATION: The Microbial Genome Program (MGP) supports key DOE business areas by providing microbial DNA sequence information that will further the understanding and application of microbiology relating to energy production, chemical and materials production, environmental carbon management, and environmental cleanup. The elucidation of microbial genome sequences is a natural outgrowth of past and current Biological and Environmental Research (BER) Programs, including DNA sequencing from the Human Genome Program, structural biology studies utilizing BER-supported facilities and synchrotrons located at DOE laboratories, and molecular microbiological research supported by BER environmental programs. The MGP benefits directly from capabilities at DOE national laboratories, DOE and National Institutes of Health Human Genome Centers, the National Center for Biotechnology Information (NCBI) at the National Institutes of Health (NIH), and the capabilities of universities and non-profits. The MGP represents a considerable interdisciplinary effort and will contribute to and draw from a wide variety of public and private programs. Over the last 5 years, sequencing of microorganisms that live in extreme environments (including the deep subsurface, geothermal environments, hypersaline environments, high-radiation environments, and toxic waste sites) has provided a considerable information base for scientific research related not only to DOE missions but also to other federal agency missions, and U.S. industry. Applications are now being sought in five complementary areas: whole-genome functional analyses, bioinformatics applied to microbial genome sequences, characterization of microbial genomic plasticity, novel microbial sequencing approaches, and the characterization of the diversity of microbial consortia and/or hard-to-culture microbes that mediate processes of relevance to the DOE. Each application must clearly state which area is being addressed; if an

applicant wishes to address more than one area, the application must clearly describe the expected advantages of an integrated approach.

Candidate microorganisms for study can comprise archaea, bacteria, or communities made up of bacteria and/or archaea that mediate or catalyze metabolic events of energy or environmental importance. Preference will be given to those applicants using microbes for which complete or near-complete genomic sequencing information in the public domain exists. (See http://www.ornl.gov/microbialgenomes/organisms.html for a current list of microbes that have been and are being sequenced.) Priority will be given to studies on those microbes that can bioremediate metals and radionuclides, microbes that can degrade significant biopolymers such as celluloses and lignins or microbes that are involved in environmental carbon management, e.g. fix or sequester CO2. Finally, microbes that participate in consortia with already-sequenced species are of interest. Strict pathogens or parasites will not be considered.

1) **Functional Analysis.** 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 published and is available for inspection. Better experimental and computational methods are needed to identify novel open reading frames and predict their functions at a whole-genome scale, particularly from completely sequenced microbial genomes. Accordingly, applications are requested that will develop better ways to interpret sequence data from novel open reading frames, and even whole genomes, using both comparative genomic approaches as well as novel analyses. The DOE MGP is particularly interested in the use of sequence data for whole genome approaches to functional prediction, functional regulation, functional categorization (e.g. transporters, environmental sensors, redox enzymes, cytoskeletal components, DNA repair systems, metal reductases, biodegradative enzymes, etc.) as well as those approaches that identify and distinguish rare or unique ORFs that can be linked to restricted environmental niches or DOE-relevant bioremediation capacities. Identification of domains in gene sequences that mediate protein- protein interactions are also of great interest. Applicants should focus on microbes of mission interest to the DOE, as described above. It is estimated that between four and six awards for a total of up to $1 million could be available for this area in FY 2001, contingent upon the availability of appropriated funds.

2) **Bioinformatics.** It is estimated that by December 2000, completed genomic sequences of perhaps 50 archaea and bacteria will be publicly available, more than a third of them as a direct result of DOE Microbial Genome Program funding. In June 2000, a draft sequence for the entire human genome became

available as well. For several microbes, complete sequences of close evolutionary relatives now or will soon exist. Computational comparative genomics can illuminate evolutionary pathways to complement traditional phenotype-based analyses, provide data for the prediction of gene function between organisms, and contribute to modeling pathways. The value of such comparative functional analysis is highlighted by the remarkable frequency of novel open reading frames in microbial genome sequences (up to half the genes in many cases) that currently lack any annotation. The evolutionary conservation of open reading frames and certain protein functions between microbes and more complex organisms (including human) emphasizes the value of microbial sequences for understanding the functions of uncharacterized microbial (and, potentially, human) genes. To this end, computational methods for interspecies genomic comparisons are an area of particular interest for this solicitation. Applications are requested that propose ways in which microbial sequence data from all sources can be analyzed, compared, annotated, and used to predict the function of homologous genes in both prokaryotic and eukaryotic organisms. Thus, this notice solicits applications for research into:

a) novel computational tools to increase the value of microbial genomic information, such as improved techniques for identifying distant sequence homologies, reconstructing phylogenetic trees, predicting gene function, or identifying and modeling gene expression networks, and

b) algorithms and tools to extract longer stretches, and make more accurate base calls from current sequencing procedures in order to assist the closure process for microbial genomes.

Of special interest will be methods that use unique DOE resources in massively parallel, high-capacity supercomputers (machines in the multi-teraflop range). 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 some level of user support will be available. It is anticipated that between three and six awards for a total of up to $2 million could be available for this area in FY 2001, contingent upon the availability of appropriated funds.

3) **Characterization of Microbial Genomic Plasticity.** Completed sequences for several microbes (e.g. Thermotoga maritima, (Nelson, K. et. al. (1999) Nature 399: 323-329) and Deinococcus radiodurans (White, O., et.al. Science (1999) 286:1571-1577) strongly suggest that entire blocks of genes have been laterally transferred during microbial evolution, even from sources in different biological kingdoms. How widespread this phenomenon may be, or any

evolutionary constraints on it, is unknown. Applications are solicited that would assess lateral gene exchanges, in terms of its frequency in different environmental niches, the mechanisms involved, as well as the circumstances in which it is observed. It is anticipated that between two and four awards totaling up to $1 million could be available for this area in FY 2001, contingent upon the availability of appropriated funds.

4) **Novel Approaches to Microbial Genomic Sequencing.** Many microorganisms that are closely related by means of phylogenetic measures (e.g., 16S rRNA comparisons) display dramatic differences in phenotypic characteristics. Such differences can be chromosomal in origin, or they can be due to extrachromosomal genetic elements. The DOE MGP is interested in novel comparative sequencing approaches that exploit the completed sequence of one microorganism to efficiently determine the sequence of a related taxon or species. This element of this solicitation could contribute to:

a) new methods to accelerate genomic comparisons, without resequencing the entire genome of the related organism de novo (technologies up to the proof-of-principle stage are eligible for support). Technologies responsive to this element of this solicitation should be firmly grounded in already completed microbial sequencing projects; these may include subtractive hybridization approaches, or "DNA chips", among others, but it is not the aim of this solicitation to support completely untested technologies;

b) strategies to more efficiently identify specific sequence features associated with phenotypic differences; and

c) techniques to characterize and quantify lateral gene transfer (especially any correlation with environmental selection).

A plan for making comparative sequence data publicly available by deposition into a community-accessible sequence database within three months of data acquisition must be included. A plan for efficient and timely annotation must be included in the Project Description. DOE expects that grantees will make all good faith efforts to publish in the open scientific literature the results of their funded work, including the genome sequences of microbes sequenced under this notice. (DOE data release requirements, a condition of any award, are available at: http://www.sc.doe.gov/production/ober/EPR/data.html). Applicants are encouraged to create process- and cost-effective partnerships that will maximize sequence data production and analysis, data dissemination, and progress towards understanding basic biological mechanisms that can

further the development of biotechnology. It is anticipated that between two and four awards totaling up to $1 million could be available for this area in FY 2001, contingent upon the availability of appropriated funds.

5) **Consortia and Hard-to-Culture Microbes.** Most of our current knowledge of microbiology is derived from individual species that either cause diseases or grow easily and readily as monocultures under laboratory conditions and are thus easy to study. The preponderance of species in the environment does neither and is thus largely unknown to science. Most are thought to grow as part of interdependent consortia in which one species supplies a nutrient necessary for the growth of another. Virtually nothing is known of the organization, membership, or functioning of these consortia, especially those involved in environmental processes in which DOE is interested. Technologies are sought that enable genomic analyses of microbial consortia as well as analyses of the genomic information content and diversity of those species that have proven refractory to laboratory culture but are plentiful in environments challenged with metal and radionuclide wastes, or involved in carbon sequestration. It is anticipated that between two and three awards totaling up to $1 million could be available for this area in FY 2001, contingent upon the availability of appropriated funds.

Preapplications

Potential applicants are strongly encouraged to submit a brief preapplication that consists of two to three pages of narrative describing the research objectives and technical approach(s). Preapplications will be reviewed relative to the scope and research needs of the OBER Microbial Genome Program, 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. A response to each preapplication discussing the potential programmatic relevance of a formal application will be communicated to the Principal Investigator within 14 to 21 days of receipt. Any renewal applications must include a list of publications resulting from previous DOE Microbial Genome Program funding.

Program Funding

It is anticipated that up to $6 million will be available for all MGP awards in Fiscal Year 2001; from twelve to as many as twenty five awards are anticipated, contingent on availability of appropriated funds in FY 2001 and the size of the awards. Multiple year funding is expected, also contingent on availability of funds and progress of the

research. Awards are expected to range from $200,000 to $1 million per year, total costs, with terms of one to three years.

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.

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 20 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 vitaes, 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", 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:

MGP 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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