

Program Announcement LAB 98-16

Genome Instrumentation Research Program

The Office of Biological and Environmental Research (BER) of the Office of Energy Research (ER) of the U.S. Department of Energy (DOE), hereby announces its interest in receiving proposals from the National Laboratories for Instrumentation Research supporting the Human Genome Program. Proposals are sought from a broad range of scientists with backgrounds in biology, chemistry, physics, and engineering including those not presently involved in the Human Genome Program. Both substantive improvements to current systems and novel and creative new strategies are needed in preparation for the needs of biology in the next century. New instrumentation and technical approaches are sought for DNA sequencing, automation and integration of DNA sequencing systems, validation of DNA sequencing accuracy, and the determination of gene function of newly sequenced DNA. The goals are to reduce costs and increase the throughput while maintaining accuracy for production DNA sequencing and related analyses.

The Office of Biological and Environmental Research of the U. S. Department of Energy and the National Human Genome Research Institute of the National Institutes of Health are participating in a coordinated international program to "determine the complete sequence of the human genome, discover all the human genes and render them accessible for further biological study." As this program continues, improvement of sequencing technology is essential to complete the sequence of the 3 billion subunits of the human genome by the target year of 2005. Functional analyses of the displayed genes and their encoded proteins will continue long thereafter.

In December of 1997 a DOE-sponsored review of the DOE Human Genome Program was published by the JASON Program Office of the MITRE Corporation. A summary and related discussion has been printed: *Science*, 279(5347), (1998) 36-37; *Science*, 279(5347), (1989) 23; and *Science*, 279(5354), (1989) 1115-1116. The full report can be accessed on the Internet using the following web address:

<http://www.ornl.gov/hgmis/publicat/miscpubs/jason/index.html>. A more general discussion of the Human Genome Program may be found in Primer on Molecular Genetics available on the Internet using the following web address:

http://www.ornl.gov/TechResources/Human_Genome/publicat/primer/intro.html.

These documents and companion references will be particularly useful to scientists and engineers less knowledgeable regarding current genomic technologies and projected needs.

Production scale sequencing has been initiated based largely on gel electrophoresis with data acquisition by laser induced fluorescence. Additionally, sequence

comparison tasks are performed using "sequencing by hybridization" technologies. However, it may not be possible to achieve the desired goal within the available budget and project period without substantial improvements in speed and reliability of sequencing methods and other techniques currently in widespread use. Continuing developments of existing approaches to address the necessities of the production environment will be required.

Further, with an eye to the future, basic research is also needed that will substantially speed and enhance genomic analyses in the years following the projected completion of the human genome in the year 2005. After this date, the need for fast and cost-effective determination of DNA sequence for the comparison of sequences among human individuals and also for the determination of the genomes of numerous organisms of biomedical and commercial interest will be ongoing. Additionally, with the continuing acquisition of this remarkable base of biological data, high throughput experimental tools will be required to assist conversion into a practical and useful understanding of the function for the encoded gene products.

Both substantial evolutionary improvements in current systems and also revolutionary technologies for the post-2005 era are sought under this program announcement.

Research proposals are invited:

- To develop approaches to more rapidly, accurately, and economically determine DNA sequence. Cost-effective approaches that increase current maximum read lengths of 800-1000 bases by at least a factor of 2.5, i.e., to at least 2000-2500 bases, are particularly desired.
- To develop instrumentation that integrates and more thoroughly automates the current steps of DNA sequence determination, e.g., sample preparation, sample loading, sample analysis, and data analysis. A priority will be placed on approaches that emphasize miniaturization and micro fabrication.
- To develop approaches that (1) verify the accuracy of a previously determined DNA sequence without having to redetermine its entire sequence and (2) provide economical error checking and proofreading of newly determined DNA sequence.
- To develop tools that enable the efficient comparison of a known DNA sequence with a related but previously undetermined DNA sequence.
- To develop techniques for determining the functions of large numbers of genes in parallel. Techniques that match the speed and volume of DNA sequence determination are particularly desired.

The success of devices, methods or techniques for DNA sequencing is dependent on downstream data technologies. Where appropriate, proposals should account for the

necessary link to current information technology and existing data sets in their plans to address the technical challenges enumerated above.

DATES: Potential proposers are strongly encouraged to submit a brief preproposal. All preproposals should be received by DOE by 4:30 P.M., E.D.T., June 8, 1998. Early submissions are encouraged. A response encouraging or discouraging a formal proposal will be communicated to the proposer within two weeks of receipt.

Formal proposals, in response to this program announcement, must be received by 4:30 p.m., E.D.T., August 19, 1998, in order to be accepted for merit review and to permit timely consideration for award in Fiscal Year 1999.

ADDRESS: Preproposals, referencing Program Announcement LAB98-16, should be forwarded to: Dr. Charles G. Edmonds, Medical Applications and Biophysical Research Division, ER-73, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290, Attn: Program Announcement LAB98-16. Preproposals will also be accepted by Fax and E-mail: Fax number: (301) 903-0567 and E-mail: charles.edmonds@oer.doe.gov.

Formal proposals, referencing Program Announcement LAB98-16, should be forwarded to: U.S. Department of Energy, Office of Energy Research, Medical Applications and Biophysical Research Division, ER-73, 19901 Germantown Road, Germantown, MD 20874-1290, Attn: Program Announcement LAB98-16. This address also must be used when submitting proposals by U.S. Postal Service Express Mail, or any commercial mail delivery service, or when hand-carried by the proposer. An original and seven copies of the proposal must be submitted.

FOR FURTHER INFORMATION CONTACT: Dr. Charles G. Edmonds, Medical Applications and Biophysical Research Division, ER-73, 19901 Germantown Road, Germantown, MD 20874-1290; telephone: (301) 903-0042; E-mail: charles.edmonds@oer.doe.gov..

Program Funding

It is anticipated that up to a total of \$2,000,000 will be available for awards to the National Laboratories to be made in Fiscal Year 1999 for the new Genome Instrumentation Research Program, contingent on the availability of appropriated funds. Award sizes are expected to be on the order of \$100,000-600,000 per year. Collaborative projects involving several research groups or more than one institution may receive larger awards if merited.

Preproposals

A brief preproposal may be submitted. The preproposal should identify, on the cover sheet, the institution, Principal Investigator name, address, telephone, fax and E-mail address, title of the project, and the field of scientific research. The preproposal should consist of a two to three page narrative describing the research project objectives and methods of accomplishment. These will be reviewed relative to the scope and research needs described in this Announcement.

Preproposals are strongly encouraged but not required prior to submission of a full proposal. Please note that notification of a successful preproposal is not an indication that an award will be made in response to the formal proposal.

Any recipient of an award from ER to perform research involving recombinant DNA molecules and/or organisms and viruses containing recombinant DNA molecules shall comply with the National Institutes of Health "Guidelines for Research Involving Recombinant DNA Molecules," which is available via the world wide web at: <http://www.niehs.nih.gov/odhsb/biosafe/nih/nih97-1.html>, (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 announcement LAB 98-16 on all submissions and inquiries about this program.

**OFFICE OF ENERGY RESEARCH
GUIDE FOR PREPARATION OF SCIENTIFIC/TECHNICAL PROPOSALS
TO BE SUBMITTED BY NATIONAL LABORATORIES**

Proposals from National Laboratories submitted to the Office of Energy Research (ER) 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 ER 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 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 12 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 ER 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
ER 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.

3.4 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 ER 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 Energy Research. 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.er.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.