

NATIONAL CENTERS FOR BIOMEDICAL COMPUTING

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Department of Health and Human Services (DHHS)

PARTICIPATING ORGANIZATION:

National Institutes of Health (NIH)

(<http://www.nih.gov>)

This RFA is developed as a roadmap initiative. All NIH Institutes and Centers participate in roadmap initiatives.

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APPLICATION RECEIPT DATE: January 23, 2004

THIS RFA CONTAINS THE FOLLOWING INFORMATION

- o Purpose of this RFA
- o Technical Assistance Workshop
- o Research Objectives
- o Organizational Structure of the National Centers
- o Mechanism of Support
- o Funds Available
- o Eligible Institutions
- o Individuals Eligible to Become Principal Investigators
- o Where to Send Inquiries
- o Letter of Intent
- o Submitting an Application
- o Supplementary Instructions
- o Peer Review Process
- o Review Criteria
- o Receipt and Review Schedule
- o Award Criteria
- o Required Federal Citations

PURPOSE OF THIS RFA

The Institutes and Centers (ICs) of the National Institutes of Health invite applications for specialized centers in the area of biomedical computing. The U54 mechanism will be used to create NIH National Centers for Biomedical Computing (NIH NCBCs). These

centers, in conjunction with individual investigator awards, will create a networked national effort to build the computational infrastructure for biomedical computing in the nation, the National Program of Excellence in Biomedical Computing (NPEBC). The establishment of the NIH NCBC was called for in the Biomedical Information Science and Technology Initiative report in 1999 (<http://www.nih.gov/about/director/060399.htm>), and their need has been reaffirmed by more recent workshops. The NIH NCBC will be devoted to all facets of biomedical computing, from basic research in computational science to providing the tools and resources that biomedical and behavioral researchers need to do their work. In addition to carrying out fundamental research, it is expected that the NIH NCBC will play a major role in educating and training researchers to engage in biomedical computing.

To build the computational infrastructure for biomedical computing in the nation, the National Program will use a combination of NIH funding mechanisms that will be supported by multiple NIH Institutes and Centers. The central constituent of the NPBEBC, the NIH NCBC, is the focus of this RFA. The NIH NCBC will provide tools and resources that biomedical and behavioral researchers can use at a variety of levels.

The NIH NCBCs will be partnerships bringing together three types of scientists: 1) computational scientists, who invent and develop efficient and powerful languages, data structures, software architectures, hardware, and algorithms for solving biomedically significant computing problems; 2) biomedical computational scientists, who adapt and deploy resources from computational science to solve significant biomedical problems; and 3) experimental and clinical biomedical and behavioral researchers, who generate data that can be transformed into knowledge by computational simulation, analysis, modeling, data mining, and visualization. These partnerships will be designed to produce, validate, and disseminate tools and computational environments that will be useful to a broad spectrum of biomedical researchers across the nation. It is expected that the partnerships will be highly interactive. Computational scientists should work with biomedical or behavioral researchers to develop the tools while the biologists validate these tools and provide feedback for the next generation of tools. In some cases, the NIH NCBCs will enhance and extend existing tools; in other cases they will develop new tools and computational environments de novo.

Individual biomedical or behavioral investigators will make use of the NIH NCBCs in different ways. Some investigators will simply use the on-line tools and services that the NIH NCBCs provide. These investigators might never have direct contact with any researchers at the NIH NCBC, but they will download software or go to the NIH NCBC web site to make use of resources found there.

Biomedical and behavioral investigators for whom a greater level of interaction with the NIH NCBC is appropriate could follow two pathways.

- 1) After the initial NIH NCBCs have been funded, NIH anticipates releasing a new program announcement that will support partnerships between individual investigators

and the centers. As an example, a biomedical research laboratory with software that is useful in modeling the function of the heart might seek to use the expertise of the NIH NCBC to modify the software to run on a computational grid. Alternatively, the biomedical researchers might seek support from the NIH NCBC to design and build hardware that would be well suited to solve their problems. Individual investigators should monitor the BISTI web site (<http://www.bisti.nih.gov>) for relevant program announcements. It is anticipated that the announcements for partnering projects will include both new RO1's and R21's and as well as competitively reviewed supplements to existing projects.

2) Individual investigators could be part of a Driving Biological Project (DBP) funded within the NIH NCBC. These projects will be described in core 3 below. An investigator who interacts with the center in this fashion will help the NIH NCBC focus its computational research on challenging biomedical problems selected for their broad biomedical significance and compatibility with the core computational expertise of the NIH NCBC. Investigators involved in a DBP will have substantial interactions with researchers at the NIH NCBC.

TECHNICAL ASSISTANCE WORKSHOP

NIH staff will conduct one technical assistance and information-sharing workshop in Bethesda, MD on November 3, 2003. This workshop will allow applicants and NIH staff to discuss and clarify any issues or questions related to this RFA. If you plan to attend the workshop, please contact Mr. Kevin Lauderdale (e-mail lauderdk@nigms.nih.gov or phone 301-451-6446) to reserve a space. Detailed information about the time and location of the meeting will be available at the BISTI web site <http://www.bisti.nih.gov>. To accommodate individuals who cannot attend the meeting, provisions will be made to distribute the information discussed. These provisions will also be posted on the BISTI web site.

RESEARCH OBJECTIVES

Increasingly, the most exciting science and the most fruitful scientific and technical approaches to biomedical and behavioral research require approaches that involve bioinformatics and computational biology as well as experimentation. To meet the infrastructure needs of modern biomedical and behavioral research, the NIH is embarking on a long-term initiative aimed at deploying an integrated national biomedical computing environment. This environment will enable the analysis, modeling, understanding, and prediction of dynamic and complex biomedical systems across time and distance scales and will allow the integration of biomedical and behavioral data and knowledge at all levels of organization. All applications in response to this announcement will be evaluated primarily for the potential of the proposed activities to contribute to this long-term goal.

This RFA provides for the establishment of NIH supported National Centers for Biomedical Computing in the service of this long-term initiative. The National Centers

will be charged with core responsibilities in implementing and coordinating a national project to make, improve, and integrate components of biomedical computing. For example a particular NIH NCBC could focus on algorithms, software development and engineering, definition of hardware requirements, and user interface development to provide an excellent computational environment for one or more classes of biomedically important computing, such as:

- o Comparative genomics
- o Biomolecular modeling and simulation
- o Analysis and modeling based on high throughput experimental techniques
- o Image analysis and reconstruction
- o Clinical trial management
- o Epidemiological analysis and modeling
- o Use of biomimetic principles in device design
- o Multiscale simulation of biological processes
- o Computational and information frameworks for integrating biological and behavioral data

Examples of computational environments that might ultimately be created could include:

- o A graphical user interface (GUI)-enabled environment that would integrate homology and motif search tools, phylogenetic profiling, proteomics and microarray analysis, and intelligent text-mining to identify of gene function and networks of interacting gene products.
- o An environment that would integrate molecular modeling and simulation tools including homology-based structural modeling, electronic structure calculations, classical molecular dynamics and Monte Carlo sampling, electrostatics, molecular docking, and stochastic dynamics, to provide the best possible inference of structure-function relationships in biomolecules.
- o A GUI-enabled environment that would integrate sequence analysis, traditional and high-throughput cell and molecular biology data analysis, clinical and behavioral data analysis, and intelligent text data mining, to understand the significance of single-nucleotide polymorphisms in determining varied response of individual patient responses to clinical interventions.
- o A software development and dissemination environment, or software framework, that would enable concurrent developer access to a moderated repository for the purpose of multi-scale organ modeling. Such an environment would allow a geographically diverse team to work on a significant biomedical problem.

The above lists are intended to be exemplary rather than exhaustive or prescriptive.

The environments should be constructed by considering the entire range of computational techniques that apply to a particular biomedical issue. In these environments all the

relevant computational techniques will be embodied in components that are robust, efficient, easy to use, widely disseminated, interoperable, versatile, in conformity with best practices in software engineering, and well tuned to the most appropriate and powerful free-standing hardware and grid computing environments. Applicants for the NIH NCBCs are encouraged to consider similar far-reaching scenarios, as a guide to long-term goals for the NIH NCBC. Although these centers as a whole will be aimed at solving a large, long-term problem, each individual center will be focused on solving smaller problems in a 5 to 10 year time frame.

ORGANIZATIONAL STRUCTURE OF THE NATIONAL CENTERS

Each NIH NCBC will be required to perform or facilitate seven different core functions: (1) conducting core research in relevant science, such as algorithm creation and optimization, creation of appropriate languages, or the creation of hardware architectures applicable to the solution of biomedical problems, (2) conducting core research and development in biomedical computational science by developing and deploying tools designed to solve particular biomedical problems, (3) establishing Driving Biological Projects (DBP) to allow experimental biomedical and behavioral researchers to interact with and drive computational research in the NIH NCBC, (4) providing infrastructure to serve the needs of the broad community of biomedical and behavioral researchers, (5) enhancing the training for a new generation of biomedical researchers in appropriate computational tools and techniques, (6) disseminating newly developed tools and techniques to the broader biomedical research community, and (7) providing an administrative core to ensure that these large centers achieve their goals within the 5 to 10 year funding lifetime of the center.

Cores 1 and 2 in an NIH NCBC should propose research that is important to biomedical or behavioral researchers and interesting to researchers in computational biology. These cores will be the largest component of the NIH NCBC. The chosen research problem should be significant, but it should also be possible to achieve substantial progress in a 5 to 10 year timeframe. It is expected that the personnel associated with core 1 will have a computer science or other mostly computational background. In contrast, it is likely that the personnel associated with core 2 will have some computational background, but they will also have a significant background in some area of biomedical or behavioral research. Cores 1 and 2 do not have to be the same size, but both must exist. While no distribution of expenditures is prescribed for the NIH NCBC, it is envisaged that cores 1 and 2 together will comprise approximately half of the overall budget.

Close and effective collaboration between the leaders of Core 1 and Core 2 is key to the success of the NIH NCBCs. The NIH NCBCs will need cutting edge computer science, as represented by Core 1, and strong leadership in translating that computer science into effective algorithms and environments for solving real biological problems. Reviewers will be instructed to evaluate applications for evidence of strong synergy between these two cores in conceptualizing, planning, and implementing the NIH NCBC. While it is not required that the leaders of core 1 and core 2 be at the same institution, applicants will have to present a convincing plan for any proposed collaboration

at a distance.

In core 3, an investigator will propose 2-4 collaborations with NIH funded biomedical or behavioral researchers to address a biomedical/behavioral question using computational approaches. It is not essential that the biomedical researchers have expertise in computational biology, but they should have a question that will drive the fundamental computational research in cores 1 and 2. The purpose of this core is to ensure that the research carried out in cores 1 and 2 has direct relevance to biomedical or behavioral research. It may be useful for these Driving Biological Projects (DPB's) to have a focus on a particular disease or organ, but that sort of focus might not be appropriate for all NIH NCBCs. It is expected that many of the biomedical researchers in core 3 will not be at the same institution as the parent NIH NCBC. In such cases, convincing plans for collaboration at a distance must be presented in the proposal. An individual DBP will last for at most three years. If the problem addressed by the DBP is not going to be completely solved in a 3 year period, the principal investigator and collaborating researchers must present plans to compete for independent funding for continuation of the work. Plans must also be presented to recruit and select additional DBPs after collaborations with the initial "founding" DBPs under the NIH NCBC have been completed. While no distribution of expenditures is mandated, it is envisaged that approximately one quarter of the budget in the NIH NCBC will be used to support the participation of the DBPs in the NIH NCBC.

The new tools that are being developed are likely to require substantial infrastructure to allow the larger community of biomedical researchers to utilize these tools. Core 4 will provide that infrastructure. Examples of the infrastructure include user support personnel, servers from which users can download software or through which users can access the software on a national or regional facility, technical support to a national or regional facility on which users use the software, or related items to enable biomedical researchers to have ready access to the products of the particular NIH NCBC.

The long-term goals of the NIH in bioinformatics and computational biology include the development of a new generation of multi-disciplinary biomedical computing scientists. In core 5, each center should propose plans to ensure that graduate students and postdoctoral fellows receive broad relevant training beyond the specific contributions they make to the infrastructure and research projects of the center. This training should occur in both directions. Students and postdoctoral fellows with a background in computational science should receive training in biomedical and behavioral science and those with a background in biomedical and behavioral science should receive training in computational sciences. In addition, plans should be presented for workshops or other activities to train the larger biomedical community about the new tools and techniques that the NIH NCBC is developing. It may be most effective if some workshops occur in the context of important biomedical or behavioral science meetings, at universities or medical schools, or using resources such as the Access Grid rather than at the NIH NCBC itself. The rationale for the structure and venue of the workshops should be carefully thought out and presented in the application.

The focus of core 6 is to disseminate new discoveries and resources to the biomedical community. Publications and a good web site are excellent ways to broadcast some of the discoveries of the NIH NCBC, but those routes may not be sufficient to inform biomedical and behavioral investigators who require guidance in pursuing computational solutions to their questions. Innovative plans to disseminate discoveries to this biomedical community should be presented in core 6. Applicants must discuss how software will be made available to the community in this core and to justify any restrictions they might place on software dissemination. Finally, plans to make data sets and databases available after funding for the NIH NCBC has ceased should be presented.

It is essential to provide an appropriate administrative structure to manage the many facets of these large, complex centers. The administrative plan should be presented as core 7. Investigators are strongly encouraged to consider proposing a project manager for the NIH NCBC. In addition to a project manager, it is expected that each NIH NCBC will have an external advisory committee. This committee should meet at least on an annual basis to review progress and offer advice. Potential members of the external advisory committee should not be contacted until after an award has been made, and these members should not be listed in the application. Core 7 should also address how the NIH NCBC will accommodate requests from individual investigators who want to make use of the centers via the anticipated individual investigator program announcements.

While no distribution of expenditures is mandated, it is anticipated that cores 4, 5, 6, and 7 will together account for approximately one quarter of the total budget of the NIH NCBC.

The NIH previously supported Planning Grants for Programs of Excellence in Biomedical Computing (pre-NPEBC) using the P20 mechanism under [PAR-00-102](#). Recipients of those awards are welcome to apply for the U54 centers in this announcement. Investigators who did not apply for or receive a pre-NPEBC award may also apply for the new U54 centers. No programmatic preference will be given either to recipients or non-recipients of pre-NPEBC awards.

MECHANISM OF SUPPORT

This RFA will use NIH U54 award mechanism. As an applicant you will be solely responsible for planning, directing, and executing the proposed project. The anticipated award date is September 15, 2004.

The ICs intend to reissue this RFA at least once to allow funded centers to have the chance for a competing continuation. This future RFA is likely to allow applications from new centers. The initial period of support for a U54 center will be five years. No center will receive more than ten years total of NIH funding.

This RFA uses just-in-time concepts. It also uses the non-modular budgeting formats. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm.

The NIH U54 is a cooperative agreement award mechanism. In the cooperative agreement mechanism, the Principal Investigator retains the primary responsibility and dominant role for planning, directing, and executing the proposed project, with NIH staff being substantially involved as a partner with the Principal Investigator, as described under the section "Cooperative Agreement Terms and Conditions of Award".

FUNDS AVAILABLE

The participating ICs intend to commit \$14 million to \$17 million in FY 2004 to fund 3 to 4 new centers in response to this RFA. An applicant should request a project period of 5 years. The budget (direct costs) may not exceed \$3 million per year. The F&A costs (sometimes known as indirect costs) of subcontractors will not count against this \$3 million limit. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size of each award will also vary. Although the financial plans of the ICs provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications.

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution has any of the following characteristics:

- o Public or private institutions, such as universities, colleges, hospitals, and laboratories
- o Units of State and local governments
- o Eligible agencies of the federal government
- o Foreign institutions are not eligible to apply for NIH NCBC centers, but foreign institutions can participate in the DPBs.

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

COOPERATIVE AGREEMENT TERMS AND CONDITIONS OF AWARD

As part of the U54 Specialized Center Grant process, the following Terms and Conditions of Award and details of the arbitration procedures pertaining to the scope and nature of the interaction between the NIH staff and the participating awardees will be incorporated into the Notice of Grant Award and provided to the Principal Investigator and

the institutional official at the time of award. These procedures will be in addition to the customary programmatic and financial negotiations that occur in the administration of grants.

Cooperative agreements are assistance mechanisms subject to the same administrative requirements as grants. The special Terms and Conditions of Award are in addition to, and not in lieu of, otherwise applicable OMB administrative guidelines, HHS Grant Administration Regulations at 45 CFR Part 74 and 92, and other HHS, PHS, and NIH grant administration policies and procedures. Cooperative Agreements are subject to the administrative requirements outlined in pertinent OMB, HHS, PHS, and NIH guidelines, with particular emphasis on HHS regulations at 42 CFR Part 52 and 45 CFR Part 74. Facilities and Administrative Cost (indirect cost) award procedures will apply to cooperative agreement awards in the same manner as for grants.

The administrative and funding instrument used for this program is a Cooperative Agreement (U54), an "assistance" mechanism (rather than an "acquisition" mechanism) in which substantial NIH scientific and/or programmatic involvement with the awardee is anticipated during performance of the activity. Under the cooperative agreement, the NIH purpose is to support and/or stimulate the recipient's activity by involvement in and otherwise working jointly with the award recipient in a partner role, but it is not to assume direction, prime responsibility, or a dominant role in the activity. Consistent with this concept, the dominant role and prime responsibility for the activity resides with the awardee(s) for the project as a whole, although specific tasks and activities in carrying out the studies will be shared among the awardees and NIH Science Officers (defined below).

Failure of the awardees to meet the performance requirements, including these special terms and conditions of award, or significant changes in level of performance, may result in a reduction of budget, withholding of support, suspension and/or termination of the awards.

1. Awardee Rights and Responsibilities

Awardees have primary authorities and responsibilities to define objectives and approaches, and to plan, conduct, analyze, and publish results, interpretations, and conclusions of their studies. The primary responsibilities of the awardees are to:

- o Define the research objectives.
- o Conduct specific studies.
- o Analyze and interpret research data.
- o Establish an External Advisory Committee for the center.
- o Provide information to the NIH Science Officer and NIH Program

Officer concerning progress.

- o Maintain career development opportunities to encourage new investigators to work in computational biology.

Awardees will retain custody of and primary rights to their data and intellectual property developed under the award subject to current government policies regarding rights of access as consistent with current HHS, PHS, and NIH policies and subject to the terms and conditions of this RFA.

Principal investigators and key personnel as appropriate are expected to participate in an annual meeting of the NIH NCBCs in the Washington, DC area. Funds for travel to the meeting should be requested in the budget.

2. NIH Responsibilities

NIH Science Officers:

NIH Science Officers will be NIH staff who will have substantial scientific involvement during the conduct of this activity, through technical assistance, advice, and coordination above and beyond normal program stewardship for grants. Each center will have one or more designated NIH Science Officer(s). A given individual may be the NIH Science Officer for more than one center. The NIH Science Officer(s) will be selected by the primary IC supporting the award. The degree of involvement by the NIH Science Officer(s) will include the following:

- o Assist in avoiding unwarranted duplication of effort across centers; help coordinate collaborative research efforts that involve multiple centers.
- o Review and comment on critical stages in the research program before subsequent stages are implemented.
- o Assist in the interaction between the awardee and investigators at other institutions.
- o Retain the option of recommending termination of studies if technical performance falls below acceptable standards, or when specific lines of research cannot be effectively pursued in a timely manner.
- o Retain the option to recommend additional research endeavors within the constraints of the approved research and negotiated budget.

To help carry out these duties, Science Officers may consult with non-NIH experts in the field.

NIH Program Officer:

NIH will appoint a Program Officer who will have program oversight responsibilities for each center. This individual will not be a Science Officer. The Program Officer will:

- o Have the option to recommend withholding support to a participating institution if technical performance requirements are not met.
- o Exercise the normal stewardship responsibilities of an NIH Program Officer.
- o Carry out continuous review of all activities to ensure objectives are being met.

3. Arbitration Process

When agreement between an awardee and NIH staff on scientific/programmatic issues that may arise after the award is made, an arbitration panel will be formed. The arbitration panel will consist of one person selected by the Director of the Center, one person selected by the NIH, and a third person selected by both NIH staff and the Director. The decision of the arbitration panel, by majority vote, will be binding. The special arbitration procedure in no way affects the right of an awardee to appeal any adverse action in accordance with PHS Regulations at 42 CFR Part 50, Subpart D, and HHS Grant Administration Regulations at 45 CFR Part 74, section 304, and HHS Regulations at 45 Parts 16 and 75.

4. Progress Reviews

The progress of the NIH NCBC will be reviewed annually by the NIH Program Officer to assure that satisfactory progress is being made in achieving the project objectives. During the first year of funding, and during subsequent years if deemed necessary by the Program Officer, reviews may be more frequent. Should problems arise in the conduct of the study, the NIH Program Officer may require that the awardee submit quarterly reports on progress and fiscal matters.

The progress report will have two components. The first will be the standard NIH progress report (Form 2590). The second will be a more specialized report that will go to the NIH Science Officer(s) and the NIH Program Officer. This specialized report should be included as an attachment to the standard progress report. The report will contain a narrative section describing the progress in each of the seven cores over the past year. The report will also contain at least two "highlights". Each highlight will be based on a publication or other product of the NIH NCBC, less than a year old, which acknowledges support from the NIH NCBC. The highlight will be written at a level that is understandable by a technically literate, but non-expert individual. The report will also contain details of the federally funded investigators that used the resources in the NIH NCBC during the preceding fiscal year. The report will also contain a list of papers

that acknowledge support from the NIH NCBC as well as publications that used the center but did not acknowledge support. These two lists of publications will be presented separately.

WHERE TO SEND INQUIRIES

We encourage inquiries concerning this RFA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

o Direct your questions about scientific/research issues to:

Greg Farber, Ph.D.
Division of Biomedical Technology
National Center for Research Resources
6701 Democracy Boulevard, Room 960
Bethesda, MD 20892-4874
Telephone: (301) 435-0778
FAX: 301-480-3659
Email: gf48a@nih.gov

Peter Good, Ph.D.
National Human Genome Research Institute
Building 31, Room b2b07
31 Center Drive, MSC 2152
Bethesda, MD 20892-2152
Telephone: (301) 435-5796
FAX: 301-480-2770
Email: pg4e@nih.gov

Eric Jakobsson, Ph.D.
National Institute of General Medical Sciences
Building 45, Room 2AS55H
45 Center Drive MSC6200
Bethesda, MD 20892-6200
Telephone: 301-594-5236
Email: ej84f@nih.gov

Peter Lyster, Ph.D.
National Institute for Biomedical Imaging and Bioengineering
6707 Democracy Boulevard
Bethesda, MD 20892-5469
Telephone: 301-402-1337
Email: pl131y@nih.gov

Milton Corn, M.D.

National Library of Medicine
6705 Rockledge Drive
Building 1 Suite 301
Bethesda, MD 20892
Telephone: 301-496-4621
Email: cornm@mail.nlm.nih.gov

o Direct your questions about peer review issues to:

Donald Schneider, Ph.D.
Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive
Bethesda, MD 20892-7806
Telephone: (301) 435-1727
FAX: (301) 480-1988
Email: schneidd@csr.nih.gov

o Direct your questions about financial or grants management matters to:

Ms. Sheryl Lane
Office of Grants Management
National Center for Research Resources
6701 Democracy Boulevard, Room 1044
Bethesda, MD 20892-4874
Telephone: (301) 435-0846
FAX: 301-480-3777
Email: LaneSh@mail.nih.gov

Ms. Linda Roberts
Grants Management
NIGMS, NIH
45 Center Drive, MSC 6200
Bethesda, MD 20892-6200
Phone: (301) 594-5141
Fax: (301) 480-2554
E-mail: robertsl@nigms.nih.gov

Mr. Dwight Mowery
National Library of Medicine
6705 Rockledge Drive
Building 1 Suite 301
Bethesda, MD 20892
Telephone: 301-496-4221
Email: moweryd@mail.nlm.nih.gov

LETTER OF INTENT

Prospective applicants should submit a letter of intent that includes the following information:

- o Descriptive title of the proposed research
- o Name, address, and telephone number of the Principal Investigator
- o Names of other key personnel including those involved with the Driving Biological Projects
- o Participating institutions
- o Number and title of this RFA

The letter of intent (and the subsequent proposal itself) should NOT include names of potential members of the proposed center's External Advisory Committee.

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows CSR staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by the date listed at the beginning of this document. The letter of intent should be sent to:

Mr. Kevin Lauderdale
Center for Bioinformatics and Computational Biology
National Institute of General Medical Sciences
45 Center Drive
Building 45, Room 2AS55D, MSC 6200
Bethesda, MD 20892-6200
Telephone: 301-451-6446
FAX: 301-480-2802
Email: LauderdK@nigms.nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a DUN and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number can be obtained by calling (866) 705-5711 or through the web site at <http://www.dunandbradstreet.com/>. The DUNS number should be entered on line 11 of the face page of the PHS 398 form. The PHS 398 document is available at <http://grants.nih.gov/grants/funding/phs398/phs398.html> in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

SUPPLEMENTARY INSTRUCTIONS:

The U54 center will be required to have seven cores: (1) conducting core research in computational science, (2) conducting core research applying computing to biomedical and behavioral problems, (3) establishing Driving Biological Projects to allow biomedical and behavioral researchers to interact with and drive research in the NIH NCBC, (4) providing infrastructure (hardware, software, and personnel as appropriate) to serve the needs of the broad community of biomedical researchers, (5) enhancing the training for a new field of biomedical researchers in appropriate computational tools and techniques, (6) disseminating newly developed tools and techniques to the broader biomedical research community, and (7) providing an administrative core to ensure that these large centers achieve their goals within the 5 to 10 year funding lifetime of the center.

It is recognized that the proposals in response to this RFA will be longer and more complex than many other NIH proposals. In order to ensure effective review, the Research plan should be divided into sections according to the above-defined cores, and separate page limits should be observed for each section.

For Core 1 and Core 2, the computer science and computational science underlying the work of the proposed NCBC, the combined total page limit is 140 pages.

For Core 3, the descriptions of the Driving Biological Projects, the total page limit is 25 pages per DBP. Since 2-4 DBPs are required, the page limits for this section are 50-100 pages.

For Core 4, establishing and maintaining an infrastructure for enabling the national community to access and utilize the tools created by the proposed NIH NCBC, the page limit is 20 pages.

For Core 5, the education and training plan of the proposed NIH NCBC, the page limit is 20 pages.

For Core 6, the plan to disseminate software, data, and new discoveries to the national community, the page limit is 20 pages.

For Core 7, the management plan for the proposed NIH NCBC, the page limit is 20 pages.

Both reviewers and program staff appreciate brevity and clarity in the application. Required information, in addition to that requested in the Form PHS 398 instructions, is listed below, by section.

Form Pages 4-5: The budget should be completed as described in the instruction sheet for Application for a Public Health Service Grant (Form PHS 398). Form Pages 4 (Detailed Budget) and 5 (Budget for Entire Proposed Project Period) should be provided for each of

cores 1, 2, 4, 5, 6, and 7. Form Pages 4 and 5 should also be provided for each of the DBPs in core 3. Each budget page should be clearly labeled.

A combined total budget for the entire center should also be prepared using Form Pages 5. This budget justification should include the justification for key personnel. As part of the justification, the percent effort that all staff spend on each core should be specified. For example, a particular postdoctoral fellow might spend 75% effort on core 1 and 25% effort on one DBP in core 3. The PI for the project must devote at least 25% of his effort to the NIH NCBC.

A justification should be supplied for equipment over \$25,000 requested for the NIH NCBC. Details of the physical location for such equipment should be provided. Similar existing equipment should also be described, and the need for the new equipment justified.

Form Pages 4 and 5 should be provided for any sub-contractual or consortium arrangements. A detailed budget justification should also be provided for such arrangements. Use continuation pages as needed.

Section 9, Research Plan D: Each of the seven cores should be described. It will be best if the applicant uses separate headings for each of these cores. Cores 1 (conducting core research in computing), 2 (conducting core research applying computing to biomedical problems), and 3 (establishing Driving Biological Projects) should be broken into appropriate subheadings.

When developing the proposal, the applicant should be aware of the following points.

The annual progress report for the U54 award will use the standard 2590 form as well as supplementary information that will be more extensive. Additional information in the progress report will include both the progress made in the center as well as the relationship between the center and collaborators. Details of the U54 progress report are spelled out in the notice of grant award and in the Terms and Conditions section of this RFA. Applications for U54 centers should contain appropriate personnel to collect the needed information and to prepare this progress report.

Because of the complexity of the NIH NCBC, program staff from NIH will likely visit periodically to conduct administrative site visits. U54 centers should be prepared for annual site visits and should budget appropriately (including travel for collaborators and other necessary costs).

Each center application is expected to include a well-developed management plan. If appropriate, the management plan should include provisions for teleconferencing or videoconferencing.

The complexity of these centers suggests that it may be necessary to request a project manager. U54 centers should budget appropriately for this manager. One of the review

criteria for these centers will be the qualifications of this project manager as well as whether the institution has an appropriate career pathway for this individual. Because of their important role, it is recommended that a project manager be listed as one of the key personnel.

Plans for the development of resources for use by the biomedical community should have appropriate timelines and mileposts. Software development should include plans and timelines for alpha testing, beta testing, production release, interface development, bug reporting, integration with other codes, extension to multiple platforms, etc.

A software dissemination plan must be included in the application. There is no prescribed single license for software produced in this project. However NIH does have goals for software dissemination, and reviewers will be instructed to evaluate the dissemination plan relative to these goals:

- 1) The software should be freely available to biomedical researchers and educators in the non-profit sector, such as institutions of education, research institutes, and government laboratories.
- 2) The terms of software availability should permit the commercialization of enhanced or customized versions of the software, or incorporation of the software or pieces of it into other software packages.
- 3) The terms of software availability should include the ability of researchers outside the center and its collaborating projects to modify the source code and to share modifications with other colleagues as well as with the center. A center should take responsibility for creating the original and subsequent "official" versions of a piece of software, and should provide a plan to manage the dissemination or adoption of improvements or customizations of that software by others. This plan should include a method to distribute other user's contributions such as extensions, compatible modules, or plug-ins. The application should include written statements from the officials of the applicant institutions responsible for intellectual property issues, to the effect that the institution supports and agrees to abide by the software dissemination plans put forth in the proposal.

Data sharing will be as important as software sharing for many National Programs. All awards made under this RFA are subject to the Final NIH Statement on Sharing Research Data (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html>).

USING THE RFA LABEL: The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: <http://grants.nih.gov/grants/funding/phs398/labels.pdf>.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the Checklist, and five signed, photocopies and all appendix materials, in one package to:

Center For Scientific Review
National Institutes Of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

APPLICATION PROCESSING: Applications must be received on or before the application receipt date listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within 8 weeks.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to an RFA, it is to be prepared as a NEW application. That is the application for the RFA must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application.

PEER REVIEW PROCESS

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by program staff in the primary IC. Incomplete or non-responsive applications will not be reviewed.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by CSR in accordance with the review criteria stated below. As part of the initial merit review, all applications will:

- o Undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed and assigned a priority score
- o Receive a written critique
- o Receive a second level review by an appropriate national advisory council or board.

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to evaluate the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. The scientific review group will address and consider each of the following criteria in assigning the application's overall score, weighting them as appropriate for each application.

- o Significance
- o Approach
- o Innovation
- o Investigator
- o Environment

The application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

SIGNIFICANCE: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

INNOVATION: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

INVESTIGATOR: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

ENVIRONMENT: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, the following items will be considered in the determination of scientific merit and the priority score:

CORES 1-3: Will the work proposed in these cores help establish an integrated national biomedical computing environment? Is the proposed work essential to establishing this environment?

CORE 3: Do the investigators have appropriate plans to obtain support for the DBPs after their support from the NIH NCBC has terminated?

CORE 4: Are the infrastructure requests adequate to meet the demands that are likely to come from biomedical or behavioral researchers?

CORES 5 and 6: Will the proposed training and dissemination tools help create a new group of multi-disciplinary or interdisciplinary investigators?

CORE 7: The reviewers will be asked to address the proposed management of the project. Will the proposed management structure allow the NIH NCBC to achieve its goals? Does the institution have an appropriate career path for the project manager? Is the mechanism to terminate old DBPs and choose new ones adequate? Will the plans to incorporate individual investigator awards work?

Reviewers should consider all seven components of the project as important, even if a particular component represents only a relatively small part of the budget. For example outreach and training, while not as costly as the core development of the computational environment, is considered to be critically important for the NIH NCBC to have the appropriate impact on biomedical research.

SOFTWARE AVAILABILITY: Does the plan for distributing the software reasonable allow wide and easy access? Are any fee structures appropriate?

DATA SHARING: The adequacy of the proposed plan to share data including the use of appropriate data standards.

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations, below).

INCLUSION OF WOMEN, MINORITIES AND CHILDREN IN RESEARCH: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria in the sections on Federal Citations, below).

CARE AND USE OF VERTEBRATE ANIMALS IN RESEARCH: If vertebrate animals are to be used in the project, the five items described under Section f of the PHS 398 research grant application instructions (rev. 5/2001) will be assessed.

ADDITIONAL REVIEW CONSIDERATIONS

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

RECEIPT AND REVIEW SCHEDULE

Letter of Intent Receipt Date: December 29, 2003
Application Receipt Date: January 23, 2004
Peer Review Date: June 2004
Council Review: September 2004
Earliest Anticipated Start Date: September 15, 2004

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

- o Scientific merit (as determined by peer review)
- o Availability of funds
- o Programmatic priorities

REQUIRED FEDERAL CITATIONS

HUMAN SUBJECTS PROTECTION: Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>

DATA AND SAFETY MONITORING PLAN: Data and safety monitoring is required for all types of clinical trials, including physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II); efficacy, effectiveness and comparative trials (phase III). The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants. (NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts, June 12, 1998: <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>).

SHARING RESEARCH DATA: Starting with the October 1, 2003 receipt date, investigators submitting an NIH application seeking more than \$500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why this is not possible. http://grants.nih.gov/grants/policy/data_sharing. Investigators should seek guidance from their institutions, on issues related to institutional policies, local IRB rules, as well as local, state and Federal laws and regulations, including the Privacy Rule.

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH: It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html>); a complete copy of the updated Guidelines are available at

http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.

The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or applications and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS: The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at

<http://grants.nih.gov/grants/funding/children/children.htm>

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS: NIH policy requires education on the protection of human subject participants for all investigators submitting NIH applications for research involving human subjects. You will find this policy announcement in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html>.

HUMAN EMBRYONIC STEM CELLS (hESC): Criteria for federal funding of research on hESCs can be found at <http://stemcells.nih.gov/index.asp> and at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html>. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see <http://escr.nih.gov>). It is the responsibility of the applicant to provide, in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s) to be used in the proposed research. Applications that do not provide this information will be returned without review.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

STANDARDS FOR PRIVACY OF INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION:

The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information", the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR). Those who must comply with the Privacy Rule (classified under the Rule as "covered entities") must do so by April 14, 2003 (with the exception of small health plans which have an extra year to comply).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (<http://www.hhs.gov/ocr/>) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html>.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and applications for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at <http://www.health.gov/healthypeople>.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance at <http://www.cfda.gov/> and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at <http://grants.nih.gov/grants/policy/policy.htm>.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

[Return to Volume Index](#)

[Return to NIH Guide Main Index](#)



Department of Health
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