This Program Announcement expires on June 2, 2004, unless reissued.

CENTERS OF EXCELLENCE IN GENOMIC SCIENCE (supercedes PAR-00-101)

Release Date: November 27, 2001

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National Human Genome Research Institute
(http://www.nhgri.nih.gov/)
National Institute of Mental Health
(http://www.nimh.nih.gov/)

Letter of Intent Receipt Dates:
For Exploratory Grants (P20): January 1, May 1, September 1
For Specialized Center (P50): April 1

Application Receipt Dates:
For Exploratory Grants (P20): February 1, June 1, October 1
For Specialized Center (P50): June 1

PURPOSE

The National Human Genome Research Institute (NHGRI) and National Institute of Mental Health (NIMH) are issuing this revised Program Announcement to modify and clarify a number of issues related to this Centers of Excellence in Genomic Science (CEGS) program. The CEGS program establishes new academic Centers for advanced genome research, using the P50 Specialized Center mechanism. Each CEGS grant supports a multi-investigator, interdisciplinary team to develop innovative genomic approaches to address a particular biological problem. A CEGS project will address a critical issue in genomic science, proposing a solution that would be a very substantial advance. Thus, the research conducted at these Centers will entail substantial risk, balanced by outstanding scientific and management plans and very high potential payoff. A CEGS will focus on the development of novel technological or computational methods for the production or analysis of comprehensive data sets, or on a particular genome-scale biological problem, or on other ways to develop and use genomic approaches for understanding biological systems. Exploiting its outstanding scientific plan and team, each CEGS will nurture genomic science at its institution by facilitating the interaction of investigators from different disciplines and by providing training of new investigators, expanding the pool of professional genomics scientists and engineers.

The formation of new groups of investigators to conduct genomic research is particularly encouraged. As some newly formed groups may require substantial time and support for development and planning before being in a position to submit a high quality Center grant application, a CEGS Planning Grant (P20) is offered to facilitate this planning.

RESEARCH OBJECTIVES

Background

The NIH, along with several other federal, private, and international organizations, is currently engaged in a multi-year research program called the Human Genome Project (HGP). Most of the initial goals of the HGP, including genetic and physical maps of the mouse and human, and the DNA sequences of *E. coli*, *S. cerevisiae*, *C. elegans*, and *D. melanogaster* have been realized. Others will be met imminently, including the complete human sequence. As of November 2001, a "working draft" of the human sequence had been

published and more than one-half of the human sequence has been finished and deposited in the public sequence databases. The complete, high quality finished human sequence will be available no later than 2003. The sequencing of the mouse genome has reached 95% coverage. By December 2001, 5-6X coverage of the genome (C57BL/6 strain) will be in the public domain and an assembly will be generated shortly thereafter. The finished, high quality sequence will be completed no later than 2005. As for the sequencing of the rat genome, coverage of greater than 1X was available as of October 2001, and 3-4X coverage is expected by 2002.

The HGP has been characterized by a focus on efficient data production, the development of new technologies, and large, comprehensive genomic data sets such as genomic maps and complete DNA sequences. Once the DNA sequence of an organism becomes available, many new avenues to studying its biology are opened. However, new and improved research tools, approaches, and capabilities are needed to discover and exploit the vast amount of biological information in complete genomic DNA sequences. In 1998, a set of new goals was adopted for the U.S. Human Genome Project (see Goals at http://www.nhgri.nih.gov/98plan/). In addition to completing the human and mouse maps and sequences, the aim of the HGP was extended to developing some of the new data sets and technological approaches that will be necessary to understand and use genomic DNA sequence.

The purpose of this solicitation is to stimulate the development of such new approaches, which are likely to involve computational, instrumental, biochemical, genetic, and analytical technologies. These approaches are likely to require the expertise of teams of investigators from different fields as well as substantial infrastructure.

The CEGS program is designed to augment NHGRI's and NIMH's grants programs. For example, previous NHGRI solicitations have supported the development of large data sets, such as genetic maps, physical maps, or DNA sequences, to meet the quantitative, resource generation goals of the HGP. While such programs continue, this new program is intended to provide support for novel basic genomics research projects. These new Centers will explore ways to conduct biological research at a genomic scale, or will develop new methods, approaches, tools, or technologies to make possible novel analyses of biological questions from a genomic perspective. Some projects may result in new analyses of existing data sets. Other projects may result in technologies and methods that provide the ability to collect, analyze, and present effectively new types of genomic data sets.

NHGRI and NIMH are committed to continuing to support basic genomic research through investigator-initiated, single-laboratory project grants, using the R01, R21, and other appropriate grant mechanisms, under existing and future programs. However, the resources needed to conduct the multi-faceted, multi-disciplinary projects that may be required to achieve significant advances in these complex problems are sometimes beyond the scope of the typical R01 grant. Therefore, the CEGS program presents an opportunity for applicants to assemble the teams of investigators from diverse disciplines that will be required to approach biological problems using genomics tools in ways that are not possible today. High priority will be given to projects that integrate multi-investigator, multi-disciplinary approaches to a focused scientific problem, especially those that can meld computational and experimental approaches.

Scope of Research

A CEGS will develop new approaches that will ultimately foster the integration of genomics with biomedical research. It must investigate new approaches to studying a biological problem, using genomic-scale (comprehensive) methods, or develop new concepts, methods, technologies, or ways to analyze data, to advance the state of the art in applying genomic approaches to biological studies. It must be tightly focused on a single biological problem or on an approach to solving biological problems.

The research plan for a CEGS must propose a very high level of innovation. The product of CEGS research is expected to dramatically enhance the biomedical research community's capabilities for conducting comprehensive, cost-effective, high throughput biomedical studies related to the DNA sequence and sequence products of organisms, with particular focus on human biology and disease. Proposing to change the way genomic science is done in the future entails a substantial level of risk, because the research will by definition not be incremental. To balance this risk, the application will present a well developed scientific and management plan to achieve a high pay-off result. Collaborations to develop genomic approaches require proficiency in several disciplines; each CEGS will engage the expertise of a multi-disciplinary team, drawing from specialists in a wide range of fields such as biology, genetics, clinical medicine, physical sciences, mathematics, computer science, and engineering, as appropriate for the project. Applications that employ state-of-the-art science that fill in knowledge but do not break new ground are unresponsive to this program.

The U.S. HGP goals for 1998-2003 (*Science*, Vol. 282, pp. 682-689, 23 Oct. 1998, see http://www.nhgri.nih.gov/98plan/) articulated several areas of genomics for which substantial research opportunities exist. The more recent publication of the Biomedical Information Science and Technology Initiative (BISTI) (http://www.nih.gov/welcome/director/060399.htm) lays out additional challenges, many of which are complementary to those of the HGP. The following excerpts from these reports exemplify the challenges and opportunities that lie ahead:

> Sequencing Technology: "In the future, de novo sequencing of additional genomes, comparative sequencing of closely related genomes, and sequencing to assess variation within genomes will become increasingly indispensable tools for biological and medical research....[R]esearch must be supported on new technologies that will make even higher throughput DNA sequencing efficient, accurate, and cost-effective, thus providing the foundation for other advanced genomic analysis tools." (HGP goals)
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> Human Genome Sequence Variation: "Natural sequence variation is a fundamental property of all genomes....Basic information about the types, frequencies, and distribution of polymorphisms in the human genome and in human populations is critical for progress in human genetics. Better high-throughput methods for using such information in the study of human disease are also needed." (HGP goals)
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> Technology for Functional Genomics: "The availability of entire genome sequences is enabling a new approach to biology often called functional genomics - the interpretation of the function of DNA sequence on a genomic scale....Many genes and other functional elements of the genome are discovered only when the full DNA sequence is known....However, knowing the structure of a gene or other element is only part of the answer. The next step is to elucidate function, which results from the interaction of genomes with their environment....Large-scale characterization of the gene transcripts and their protein products underpins functional analysis....Improved technologies are [also] needed for global approaches to the study of non-protein-coding sequences...." (HGP goals)
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> Comparative Genomics: "Because all organisms are related through a common evolutionary tree, the study of one organism can provide valuable information about others. Much of the power of molecular genetics arises from the ability to isolate and understand genes from one species based on knowledge about related genes in another species. Comparisons between genomes...provide insight into the universality of biologic mechanisms and....into the details of gene structure and function." (HGP goals)
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> Bioinformatics and Computational Biology: "Bioinformatics support is essential to the implementation of genome projects and for public access to their output....Collection, analysis,

annotation, and storage of the ever increasing amounts of mapping, sequencing, and expression data in publicly accessible, user-friendly databases is critical to the project's success. In addition, the community needs computational methods that will allow scientists to extract, view, annotate, and analyze genomic information efficiently." (HGP goals)

"To make optimal use of information technology, biomedical researchers need, first of all, the expertise to marry information technology to biology in a productive way. New hardware and software will be needed, together with deepened support and collaboration from experts in allied fields. Inevitably, those needs will grow as biology moves increasingly from a bench-based to a computer-based science, as models replace some experiments and complement others, as lone researchers are supplemented by interdisciplinary teams. The overarching need is for an intellectual fusion of biomedicine and information technology." (BISTI goals)

"The information that biomedical researchers are amassing in profuse quantities today...creates enormous digital repositories of information. The scale of those databases swamps all the information collected before....In order to be useful, the data must be indexed and stored, and the challenges for data analysis and abstraction are formidable." (BISTI goals)

The passages quoted above from the U.S. HGP five-year plan and the BISTI report are intended to convey the kinds of subjects that may be appropriate under this Centers program. This PA does not provide a list of examples of possible Center themes because of the desire not to limit applicants' imaginations and to solicit truly new ideas for genomic approaches to biological problems, as they pertain to the goals discussed above. Investigators who wish to propose developing such novel approaches are strongly encouraged to discuss their ideas with program staff prior to submitting an application, to ensure that applications will be responsive to the CEGS program.

Biomedical research has entered an era in which the solutions to many important problems requires the collection and analysis of large data sets, such as an entire genome, an entire set of expressed RNAs or proteins, an entire gene family from a large number of species, the variation among individuals for a genomic region of substantial size, or a class of gene regulatory or chromatin organizational elements. Therefore, the unifying theme for this program will be that the Centers will address important biological problems on a "genomic scale." In this context, the term "genomics" is not limited to studies directly related to DNA sequence, but instead encompasses global, comprehensive, high-throughput, cost-effective approaches to studying biological systems, including for example DNA, RNA, proteins, metabolites, and regulatory and biochemical pathways and networks. The genomic approaches and technologies that are proposed to be developed under CEGS support should be applicable to a wide variety of cell types or organisms, and usable in a global, high-throughput, cost-effective manner. Methods and concepts that are applicable only to a particular genetic locus, disease, or organ system will not be supported under this program. Model systems, such as a limited number of gene families, regulatory networks, or pathways, may be used to develop the genomic approach, as long as the approach is scalable and broadly applicable. The grant application must clearly justify how the model study will be expandable beyond the particular model(s) used in the developmental research, to ultimately support global analyses. For example, if a particular pathway is being modeled, the application must explain how the modeling algorithms will be extended to other pathways. To the extent that cost-effective, global approaches can be developed and also applied within the context of the CEGS budget, such application of the new approach is acceptable. However, the budget limits under this PA may preclude both developing and globally applying the genomic approach that is the subject of the research.

NIMH is especially interested in novel genomic approaches that have high potential for accelerating our understanding of the genetic basis of the nervous system and mental disorders. Thus, these systems may provide appropriate models for developing the genomic approach, as described above, and similarly, CEGS project outcomes are generally expected to advance these goals because of their broad applicability.

Cost and data quality are central issues in the development and application of genomic approaches. Therefore each CEGS must address these factors as it develops its grant application and implements those plans under CEGS support. These cost and quality concerns must be addressed both in terms of any utilization of conventional technologies for the collection of trial data sets within the CEGS research plan (if such data collection is required), and of the manner in which novel technologies and concepts generated by the CEGS would be applied in the future. The cost of collecting global data sets is often very high; therefore, a CEGS application to very significantly reduce the cost of collecting a data set that, today, can be collected only at great expense, could be substantially enabling to the genomics community, and is therefore considered responsive to this PA.

It is anticipated that a CEGS may employ large amounts of data to accomplish its goals. However, the application of genomic technologies for data production per se is not the purpose of a CEGS, and the CEGS program is not intended primarily to build infrastructure for the application of current genomics technologies. Applicants may use data sets collected under other funding, if the CEGS project purpose is to develop novel, integrated analyses that extend the interpretation and utility of those data. Decisions by NIH to embark on the large-scale implementation of any new tools developed by a CEGS to generate large data sets will require careful consideration, with advice from the scientific community.

Leveraging of genomic resources: Preference will be given to the development of genomic methods for eukaryotes where genome sequence is available. Methods development or pilot studies using other systems (e.g., eukaryotes whose genomes have not been sequenced, or prokaryotes for which the genomic sequence is known) will be considered with adequate justification; direct applicability of methods and concepts developed in such a project to the analysis of eukaryotic genomes must be evident. Where appropriate, integration with other NIH genomics initiatives (e.g., NHLBI genomics program [http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-99-024.html], full-length cDNA [http://mgc.nci.nih.gov/], and SNPs [http://www.nhgri.nih.gov/About_NHGRI/Der/SNPawardees.htm]) will be considered advantageous.

Training Objective

Each CEGS application is required to have a training component that leverages the strengths of the Center and its investigators to train the next generation of interdisciplinary scientists who will bring creative approaches to studying biological problems through a genomic approach. There is a widely recognized shortage of investigators who have the interdisciplinary skills needed to conduct most effectively the types of genome-scale research described in this PA.

> "The HGP has created the need for new kinds of scientific specialists who can be creative at the interface of biology and other disciplines, such as computer science, engineering, mathematics, physics, chemistry, and the social sciences. As the popularity of genomic research increases, the demand for these specialists greatly exceeds the supply. In the past, the genome project has benefited immensely from the talents of non-biological scientists, and their participation in the future is likely to be even more crucial. There is an urgent need to train more scientists in interdisciplinary areas that can contribute to genomics. Programs must be developed that will encourage training of both biological and non-biological scientists for careers in genomics....[A] stable academic environment for genomic science must be created so that innovative research can be nurtured and training of new individuals can be assured." (HGP goals)
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> "Strong action by the NIH is required because the existing biomedical research and teaching structures of the universities and research institutions of this country inadequately value interdisciplinary efforts generally, and computation in particular. Few grant programs and fewer academic departments foster the kind of interdisciplinary work required to meet biomedical challenges, let alone educate students about them. National Programs specifically would include

formal and informal instruction from the undergraduate through post-graduate levels, and incorporate a range of opportunities for scholars and researchers to participate." (BISTI goals)

One reason for the lack of adequately qualified personnel is that there are too few appropriate environments available to support this kind of training. The CEGS program is intended to help to alleviate this shortage by supporting the development of Centers that can serve as academic foci for genomics, and thereby to increase the cadre of investigators qualified to participate in the development of new genomics approaches to biomedical research.

To maximize the impact of these new Centers, they should integrate the training of new investigators and broaden the training of established investigators. This might include plans to recruit into genomics investigators already trained and accomplished in other fields of research and engineering. Graduate students and postdoctoral fellows, at a minimum, should participate in the research; however, such participation alone will be considered insufficient to meet the training goals of the CEGS program. NHGRI and NIMH expect applicants to develop creative approaches, using a combination of the standard training vehicles used by academic institutions (e.g., training grants, fellowships, seminar programs, course work) and more novel avenues. This training program should take advantage of unique aspects of the research program, the combination of investigators' talents, and other unique institutional resources that underpin the CEGS, to offer innovative, substantive training opportunities for pre-doctoral students, post-doctoral fellows, and other investigators. The CEGS will therefore become an additional opportunity, beyond those previously developed by NHGRI and NIMH (see http://www.nhgri.nih.gov/Grant_info/Funding/Training/), for expanding the cadre of investigators working in the field of genomics.

NHGRI and NIMH are committed to increasing the number of individuals from underrepresented minority groups who have the training to pursue careers in genome and ELSI research. NHGRI has conducted workshops to develop goals, plans and resources, to aid in the development of such training programs. The action plan which was developed by the staff and approved by the National Advisory Council for Human Genome Research in May 2001 strongly encourages the NHGRI staff and its grantees to work cooperatively in increasing the number of underrepresented minorities involved in genomics research. This information is available from
http://www.nhgri.nih.gov/Policy_and_public_affairs/Minority_Activities/minority_planning.htm

Genome research offers tremendous challenges and opportunities for improving human health and ELSI research offers the chance to explore some of the most profound ethical, legal and social issues of our time. There are extraordinary career opportunities in genome and ELSI research in which all should share.

The scope and importance of research conducted in CEGS is anticipated to provide an outstanding opportunity for the training of underrepresented minority scientists. Moreover, the research infrastructure of CEGS institutions provides ideal training environments for short- and long-term training opportunities. NHGRI and NIMH actively encourage all CEGS programs to include training of underrepresented minorities at all career levels in their research. Therefore, in the context of the overall training plan, applicants should describe their specific plans for training of underrepresented minorities.

ELSI Objective

For CEGS research projects that raise substantial ethical, legal, or social concerns (e.g., the study of sequence variation in specific populations), a component of the Center focusing on analysis of such concerns as they relate to the particular research proposed is strongly encouraged. To be considered for funding as part of the CEGS grant, the ELSI research must be effectively integrated with and highly relevant to the research plan. Current information on the NHGRI ELSI program is available at
http://www.nhgri.nih.gov:80/About_NHGRI/Der/Elsi/ Please note that CEGS applications are not required to have an ELSI component.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators. Applications from foreign institutions and for-profit organizations will not be accepted; however, subcontracts to foreign institutions and for-profit organizations will be considered.

MECHANISM OF SUPPORT

This PA will use the National Institutes of Health (NIH) P50 Specialized Center and P20 Exploratory Grant mechanisms. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant.

For administrative reasons all applications received in response to this solicitation will be initially assigned to NHGRI. After discussions between the two participating NIH Institutes and after review and prior to award, the most programmatically relevant applications may be reassigned to NIMH. All funded applications, regardless of their eventual assignment, will be managed administratively in accordance with the goals and objectives established by NHGRI for the CEGS program.

P50 Specialized Center Grants

A P50 Center grant application may request up to five years of support. The length of award will be determined through the peer review and Council advisory processes. Genomics is a rapidly changing field, and it is anticipated that most projects that can be initiated now are likely to have a limited lifetime during which support as a CEGS will be appropriate, either because the project goals will have been accomplished or the Center will have developed to the point that support from another source will be more appropriate. Therefore, the total length of support for any P50 Center under this program will not exceed ten years.

In general, each CEGS will receive an administrative site visit during the third year of each competing cycle. The fifth year of funding will depend on the outcome of that administrative review, and the Principal Investigator (P.I.) will receive advice about the NHGRI's and NIHM's interest in accepting a competing renewal application to extend the initial award.

The requested budget for a CEGS may be up to $2 million direct costs for the first year for continuing operations (e.g., personnel, standard laboratory equipment, supplies, travel and other expenses). Future year budgets may exceed $2M for inflationary adjustments. Under this cap, it is anticipated that the size of the awards will vary because the nature and scope of research programs will vary. To accommodate collaborations that extend beyond single institutions, Facilities & Administrative (F&A) charges on the subcontracts, which are formally direct costs to the parent institution, will be excluded in considering the $2M operating costs limit. Because of the unusual nature of these Centers, they may need to acquire specialized equipment. Funds for such specialized equipment may be requested in excess of the $2 million operating costs limit if very well justified. Specialized equipment in excess of $500,000 over the life of the grant will generally not be permitted. NHGRI and NIMH anticipate establishing ten or more CEGS over the next few years, and therefore expect that two to four P50 awards will be made per year. The actual number of awards and level of support will depend on receipt of a sufficient number of applications of high scientific merit and availability of funds.

P20 Planning Grants

A high priority under this program is the establishment of new academic Centers in which state-of-the-art genomics research can be conducted. At some institutions, the nucleus of a well-functioning collaborative research group that could conduct the research described in this PA may already exist, and such groups will be able to submit suitable P50 applications for this program directly. However, some groups of investigators may require an opportunity to collect preliminary data, enhance their collaborative network by strengthening and establishing new multi-investigator or interdisciplinary relationships, demonstrate effective collaborations, explore organizational concepts, develop courses or curricula, or refine and fully develop the vision of the proposed P50 CEGS project. The Exploratory Grant (P20) mechanism should be used when the applicant wishes to request a period of planning and preliminary investigation prior to preparing a P50 Center application. The planning grant application must explicitly demonstrate how the planning grant activities will lead to the P50 application, and describe in substantial detail a vision of the research to be conducted under the subsequent P50 grant. The planning grant budget may request funds for partial salary of key investigators, travel, and some supplies and equipment. Planning grants will be awarded for up to three years and up to $150,000 direct cost per year. A planning grant is not required as a precursor to a P50 Center application. Funding of a planning grant does not obligate NHGRI to fund a subsequent P50 Center grant.

GUIDANCE FOR APPLICANTS FOR P50 CENTER GRANTS

Innovative Genomic Approach

The applicant should identify clearly in the abstract and more fully in the research plan the new capabilities that are proposed to be developed, and the specific biological context in which those capabilities will be developed and studied, as a result of the establishment of the Center. The synergies achieved through the establishment of multi-disciplinary teams and collaborations should be fully described, as these are central requirements for the establishment of a CEGS.

Each of the items listed below must be addressed in clearly labeled sections of the application: Management and Organization, Training Plan, ELSI Research Plan (if included), Data and Materials Dissemination Plan, Human Subjects, and Vertebrate Animals. These sections are in addition to the 40 page Research Plan (sections a-d; see APPLICATION PROCEDURES, below).

Management and Organization

A successful P50 grant application will include a well-integrated project plan. The grant application should describe the specific administrative and organizational structure that will be used to support the research, and the synergies enabled by this structure. CEGS projects will be multi-disciplinary and will draw on a variety of resources. Thus, a well thought-out and carefully described organization will be required. If core facilities or shared resources are required, these should be described, as should their management and service to the research projects.

The application should explain how different components of the organization, including key personnel, will interact, why they are essential to accomplishing the overall goal of the research, and how the combined resources create capabilities that are more than the sum of the parts. Very clear evidence that the key investigators will collaborate effectively must be presented in the application. If such evidence cannot be provided, a P20 planning grant is recommended for launching the project. "Centers-without-walls" are welcome under this solicitation. However, if any component of a proposed Center is physically separated from the others (i.e., in a different department or institution), the application must address how the effects of that separation will be managed. The NHGRI is not specifying a particular organizational structure for a CEGS, as each applicant should develop the structure that would best promote the proposed research.

However, note that the effectiveness of the proposed structure will be a criterion of the evaluation prior to an award and its implementation will be monitored after an award is made.

The P.I. is responsible for ensuring that scientific goals are met and for developing and managing a decision-making structure and process that will allow resources to be allocated (and reallocated, as necessary) to meet those goals. To be successful, projects of the complexity, both scientific and managerial, that participating institutes anticipate will characterize a CEGS require a substantial amount of the P.I.'s effort. Therefore, the P.I. will be required to devote at least 30% effort to the leadership and implementation of the Center.

A timeline for the project should be presented. This timeline should outline how the project's goals can be met within the time frame of a CEGS grant. The timeline will also assist the investigators, NHGRI and NIMH, and their advisors in evaluating progress toward the project's goals. For those projects for which the investigator deems it appropriate to do so, applicants are encouraged to present explicit, quantitative milestones.

Training Plan

Referring to the training goals described above, this section of the application will describe the training plan, and how the proposed CEGS training component would broaden the "expert" base of genomics research scientists. Training of underrepresented minority individuals, women, and persons with disabilities is a high priority and must be described in detail.

Data and Materials Dissemination Plan

The sharing of materials, data, methods, and software in a timely manner has been an essential element in the rapid progress that has been made in genome research. Early in the project, the advisors to the NIH and the Department of Energy (DOE) genome programs encouraged more rapid sharing than had been practiced in most biological research (http://www.nhgri.nih.gov/Grant_info/Funding/Statements/data_release.html). This has become the standard for genome research. In fact, attention to the importance of rapid and wide dissemination of research tools has expanded beyond the genome community. The NIH, as a whole, is interested in ensuring that the information about new methods, technologies, computer software, and as many data developed through federally-sponsored research as possible becomes readily available to the research community for further research and development. With the expectation that this will stimulate additional research and thus lead more rapidly to information and products that improve the health of the public, the NIH has recently issued a set of Principles and Guidance that address the issue of data release (http://ott.od.nih.gov/NewPages/RTguide_final.html).

This guidance is an integral part of the philosophy of rapid data release in the CEGS program for any large-scale data collection. To the extent that established public databases (e.g., GenBank and dbSNP) have the capability for collecting and disseminating the data that would be collected under a CEGS grant, a plan for the rapid deposition of data into such public databases should be presented in the application. If the established public databases cannot be used for this purpose, applicants should develop and propose specific plans for sharing the data generated through the grant. Similarly, applicants should propose specific plans to share materials, methods, technologies, and software generated through the grant.

The technology transfer practices and policies of the applicant institution, as they relate to resources anticipated to be developed through NIH support of the proposed project, should be described in the CEGS application. If the collaborations supported under the grant will involve commercial entities, the effect this will have on widespread and rapid dissemination of data and materials produced under federal support should also be described. It is to the advantage of applicants and their collaborators to have reached agreement as early as possible on issues related to technology transfer and data and materials dissemination, and to describe these plans in the application. Under NIH grants policy, the grantee institution cannot provide funds

to collaborating entities until subcontracts have been negotiated. Additionally, peer reviewers, NHGRI and NIMH staff, and advisors will evaluate the adequacy of dissemination plans prior to award (see below). Please note that institutional sign-off on the grant application signifies that all relevant components of the institution, including the technology transfer office, have reviewed and approved the document.

The initial review group will comment on the appropriateness of the proposed plan for data and materials dissemination. NHGRI and NIMH advisors and staff will also consider the adequacy of the dissemination plan as one of the criteria for award. The proposed sharing plan, after negotiation with the applicant when necessary, will be made a condition of the award. Evaluation of competing renewal application and annual non-competing progress reports will include assessment of the responsiveness to NIH guidelines of data, materials, methods, and software dissemination practice by the grantee.

Human Subjects

The PHS 398 form describes the information that must be included in the application, section e, concerning the protection and inclusion of human subjects in research. Note that a recent change in NIH policy no longer requires the applicant to obtain Institutional Review Board (IRB) approval prior to submission or review of the application. Instead, IRB approval is required before an award is made.

Vertebrate Animals

The PHS 398 form describes the information that must be included in the application, section f, concerning the use of vertebrate animals. Note that IACUC approval must be obtained before the application can be reviewed.

LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent that includes a descriptive title of the proposed research, the name, address, telephone number, and e-mail address of the principal investigator, names of other key personnel and, if applicable, participating institutions, and the number and title of this PA. Although a letter of intent is not required, is not binding, and does not enter into the review of subsequent applications, the information that it contains allows NHGRI staff to estimate the potential review workload and plan the review. Applicants planning to request $500,000 or more in direct costs for any year must receive authorization from NHGRI program staff at least six weeks before submitting the application (see ADDITIONAL APPLICATION PROCEDURES FOR P50 CENTER GRANTS, below).

The letter of intent is to be sent by e-mail to:

Jeffery A. Schloss, Ph.D.
Division of Extramural Research
National Human Genome Research Institute, NIH
TEL: (301) 496-7531
FAX: (301) 480-2770
Email: jeff_schloss@nih.gov

APPLICATION PROCEDURES (P50 AND P20)

The PHS 398 research grant application instructions and forms (rev. 5/2001) at http://grants.nih.gov/grants/funding/phs398/phs398.html must be used in applying for these grants and will be accepted at the application deadlines indicated on the first page of this PA. This version of the PHS 398 is available in an interactive searchable format. Beginning January 10, 2002, the NIH will return applications

that are not submitted on the 5/2001 version. For further assistance contact Grants Info, Telephone 301/435-0714, Email: GrantsInfo@nih.gov.

The P20 grant applications will have the standard 25 page limit for Research Plan sections a-d.

The title and number of the PA must be typed on line 2 of the face page of the application form and the YES box must be marked.

Submit a signed, typewritten original of the application, including the Checklist, and three signed photocopies 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)

At the time of submission, two additional copies of the application, including all appendices, must be sent to:

SCIENTIFIC REVIEW BRANCH
NATIONAL HUMAN GENOME RESEARCH INSTITUTE, NIH
BLDG. 31, ROOM B2-B37
BETHESDA, MD 20892-2032
TEL: (301) 402-0838
FAX: (301) 435-1580

ADDITIONAL APPLICATION PROCEDURES FOR P50 CENTER GRANTS

The page limit for applications using the PHS 398 form will be expanded to 40 pages for Items a-d of the Research Plan, for CEGS P50 applications. In addition to the 40 page Research Plan, the following separate sections are to be included in the application, observing the stated page limits: The Management and Organization Plan, Training Plan, and Data and Materials Dissemination Plan, combined, may not exceed 12 pages. The ELSI plan, if included, may not exceed 5 pages.

In accordance with NIH policy (NIH Guide for Grants and Contracts, October 16, 2001, available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-004.html), an applicant planning to submit a new (type 1), competing continuation (type 2), competing supplement, or any amended/revised version of the preceding grant application types requesting $500,000 or more in direct costs for any year MUST contact NHGRI program staff before submitting the application, as plans for the study are being developed, to obtain agreement that NHGRI will accept the application for consideration of an award. Permission to submit the application must be granted at least six weeks before the grant application deadline. The applicant must identify, in a cover letter sent with the application, the NHGRI staff member who agreed to accept assignment of the application. The NHGRI is not obligated to accept applications requesting more than $500,000 in the absence of timely staff agreement.

This policy requires an applicant to obtain agreement for acceptance of both any such application and any such subsequent amendment. Refer to the NIH Guide for Grants and Contracts, October 16, 2001, available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-004.html

ADDITIONAL APPLICATION PROCEDURES FOR P20 PLANNING GRANTS

The PHS 398 form will be used with the usual page limits. The planning activities to be carried out, and the justification for their necessity, should be described in the context of the anticipated P50 Center grant application. Describe the research plan for collection of preliminary data, and the scientific planning that will ensue to develop the full P50 grant application. Describe the activities to strengthen the interdisciplinary team of researchers, to develop the management structure for the P50 Center, and to develop the courses, curriculum, and other options that will be included in the training plan.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by CSR and for responsiveness by the NHGRI. Incomplete and/or unresponsive applications will be returned to the applicant without further consideration. Applications that are complete and responsive to the PA will be evaluated for scientific and technical merit by an appropriate peer review group, convened by the NGRI in accordance with the standard NIH peer review procedures. The applications will receive a second-level review by the National Advisory Council for Human Genome Research and the National Advisory Mental Health Council, as appropriate.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. To ensure that applications for this CEGS program are evaluated appropriately, the standard NIH review criteria have been adapted to be more appropriate for applications of the scope described in this PA. In the written comments reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be considered in assigning the overall score, weighting them as appropriate for each application. Note that 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, however, for this program, a high level of innovation will be required of all applications.

Review Criteria for P50 Centers

(1) Significance: Importance of the proposed research areas and topics being explored, and their relevance to investigation of biomedical problems that can be studied using genomic approaches. Utility to other researchers of any technology, research tools, software, scientific approaches, methods of analysis, etc. that are proposed to be developed. Likely effect of the proposed research on the field, and likely usefulness to the larger biological community.

(2) Approach: Quality of the scientific research plan. Likelihood that the proposed research plan will achieve the aims of the proposed research and will substantially improve the methodological or conceptual approach to the problem. Appropriateness of the proposed experimental approach, conceptual framework, design, methods, analyses, techniques, and technologies to the proposed research. Acknowledgement of potential problems and consideration of alternative approaches. For proposed multi-component Centers, the scientific gain from combining the research components in a Center, i.e., the degree of interrelatedness and synergy among the components. If any individual component were removed, would the ability of the CEGS to accomplish its overall aims be impaired? Plans for monitoring and ensuring data quality and cost reduction. Appropriateness of timeline and milestones.

(3) Management: Appropriateness and quality of the management plan, including the effectiveness of the management structure. Quality of the plan for deployment of fiscal resources, equipment and human resources to attain the research aims and overall CEGS goals. Organization and coordination of the personnel. Quality of the plans for making critical decisions or choices about overall research direction

during the project. Where appropriate, the cost-effectiveness of approaches used or under development to implement the research plan.

(4) Innovation: Novelty or originality of approach, method, technology, experimental design (including presentation, organization, analysis or application of data), conceptual framework, or the insight provided into a genomic approach to a biological problem.

(5) Investigators: Appropriateness of the scientific training, background, and expertise of the Principal Investigator and key personnel to achieving the specific aims and overall goals of the proposed research. Contribution that the individual and combined scientific expertise of the key personnel will make to the achievement of the overall goals of the proposed research. Adequacy of the P.I.'s ability to lead and coordinate the activities, and develop and implement the management plan, as required for the project's success. Adequacy of the level of effort of key personnel. Evidence of effective collaboration among key personnel. Formulation of a multi- or inter-disciplinary team that brings novel capabilities to the research program.

(6) Environment: Adequacy of the scientific environment and resources available, including space, equipment, services, infrastructure, and facilities. Degree to which the proposed research plan, experiments, or organization take advantage of unique features of the scientific environment. Degree of institutional commitment, including any needed expansion of facilities, improvement of infrastructure, and relief from other academic duties where necessary. Environment for training or educational activities.

(7) Data release and distribution of research tools: Adequacy of plans for dissemination to the scientific community of research tools or research resources (e.g., data sets, computer software, mutant stocks, DNA libraries), methods, and technologies that are proposed to be developed.

(8) Training: Quality of the proposed training plan and its likely effectiveness in producing well-trained researchers who can develop new genomics approaches and apply them to biological problems. Plans to develop new training opportunities and to integrate them with other on-going or planned training. Plans to achieve effective training of underrepresented minorities will receive particular attention.

(9) ELSI: If plans include an ELSI project, quality of the research plans for the proposed ELSI project, its ability to leverage the scientific resources of the project, and its effective integration into the research activities of the CEGS.

Review Criteria for P20 Planning Grants

(1) Significance: Importance of the proposed research areas and topics being explored, and their relevance to elucidating a biological problem, particularly one that is amenable to genomic approaches. Effect of the proposed areas of research on the field, and the likely impact on the larger biological community.

(2) Approach: Quality of the scientific research plan. Likelihood that the proposed planning grant will culminate in the ability to submit a high quality CEGS P50 grant application, through, for example, the development of on-going collaborations and generation of relevant preliminary data, and crystallization of research approaches.

(3) Management: Quality of the plan for acquisition, organization, and deployment of equipment and human resources to attain the goals of the exploratory research. Potential success of the proposed exploratory components. Adequacy of the level of effort of key personnel.

(4) Innovation: Novelty or originality of the research area being investigated or the methods to be developed.

(5) Investigators: Appropriateness of the training, background, and expertise of the P.I. and key personnel to achieving the specific aims and overall goals of the proposed research.

(6) Environment: Adequacy of the scientific environment and resources available, including space, equipment, services, infrastructure, and facilities. Degree to which the proposed research plan, experiments, or organization take advantage of unique features of the scientific environment. Degree of institutional commitment, including any needed expansion of facilities, improvement of infrastructure, and relief from other academic duties where necessary. The environment for training and educational activities.

(7) Data release and distribution of research tools: Adequacy of plan to develop a responsive data and tools distribution plan, taking into account all of the issues raised in the relevant section of this announcement.

(8) Training: Adequacy of plan to develop an effective training component.

(9) ELSI: If plans include an ELSI project, quality of the plans to develop an ELSI project that leverages the scientific resources of the project, and its effective integration into the research activities of the CEGS.

Additional Review Criteria for P50 and P20 Applications

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

> If the application proposes to involve human subjects or study human tissue samples, exempt or not, then the adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research will be evaluated. Plans for the recruitment and retention of subjects will also be evaluated.
>
> The reasonableness of the proposed budget and duration in relation to the proposed research.
>
> The adequacy of the proposed protection for human subjects, animals, or the environment, to the extent they may be adversely affected by the project proposed in the application.

AWARD CRITERIA

Applications will compete for available funds with all other recommended applications received through this and other NHGRI and NIMH programs. The following will be considered in making funding decisions: Quality of the proposed project as determined by peer review; appropriateness of plans for sharing data, materials, methods, and technology; availability of funds; and programmatic balance and priority.

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 PA, Centers of Excellence in Genomic Science, 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/.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

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 AMENDMENT "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 proposals 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

It is the policy of NIH 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 was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not98-024.html

Investigators also may obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

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 proposals for research involving human subjects. This policy announcement is found in the NIH Guide for Grants and Contracts Announcement dated June 5, 2000, at the following website: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

URLS IN NIH GRANT APPLICATIONS OR APPENDICES

All 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. Reviewers are cautioned that their anonymity may be compromised when they directly access an Internet site.

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.

INQUIRIES

Inquiries are strongly encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

Jeffery A. Schloss, Ph.D.
Division of Extramural Research
National Human Genome Research Institute, NIH
TEL: (301) 496-7531
FAX: (301) 480-2770
Email: jeff_schloss@nih.gov

Direct inquiries regarding scientific issues on the application of genomic approaches to the nervous system and mental disorders to:

Steven O. Moldin, Ph.D.
Division of Neuroscience & Basic Behavioral Science
National Institute of Mental Health, NIH
TEL: (301) 443-2037
FAX: (301) 443-9890
E-mail: smoldin@mail.nih.gov

Direct inquiries regarding review issues to:

Scientific Review Branch
National Human Genome Research Institute, NIH
TEL: (301) 402-0838
FAX: (301) 435-1580
E-mail: rp7s@nih.gov

Direct inquiries regarding fiscal matters to:

Jean Cahill
Grants Administration Branch
National Human Genome Research Institute, NIH
TEL: (301) 402-0733

FAX: (301) 402-1951
E-mail: jc166o@nih.gov

Direct inquiries regarding fiscal matters for projects on the application of genomic approaches to the nervous system and mental disorders to:

Carol J. Robinson
Grants Management Branch
National Institute of Mental Health, NIH
TEL: (301) 443-3858
FAX: (301) 443-6885
E-mail: crobinso@mail.nih.gov

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance Nos. 93.172 (NHGRI) and 93.242 (NIMH). Awards are made under authorization of sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies and Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-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, and 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.