

Membrane Protein Production and Structure Determination

RFA Number: RFA-RM-04-026

Part I Overview Information



Department of Health and Human Services

Participating Organizations

National Institutes of Health (NIH) (<http://www.nih.gov/>)

Components of Participating Organizations

This RFA is Developed as a Roadmap Initiative. All NIH Institutes and Centers Participate in Roadmap Initiatives.
This RFA will be administered by NIGMS on behalf of the NIH.

Announcement Type:

New

Catalog of Federal Domestic Assistance Number(s)

93.859

Key Dates

Release Date: October 21, 2004

Letters Of Intent Receipt Date(s): December 23, 2004

Application Receipt Dates(s): January 24, 2005

Peer Review Date(s): June/July, 2005

Council Review Date(s): September, 2005

Earliest Anticipated Start Date: September, 2005

Additional Information To Be Available Date (Url Activation Date): None anticipated.

Expiration Date: January 25, 2005

Due Dates for E.O. 12372

Not Applicable

Executive Summary

This RFA solicits applications to enhance the rate of membrane protein structure determination and to facilitate the determination of membrane protein structures. Methods development for expression, oligomerization, solubilization, stabilization, purification, characterization, crystallization, isotopic labeling of membrane proteins, and for determination of their structures by electron microscopic, x-ray diffraction, nuclear magnetic resonance (NMR) and mass spectrometry, and other biophysical techniques are emphasized.

- The total amount to be awarded is \$5 million in FY05.
- The numbers of individual awards will depend on the types of awards made.
- The anticipated number of awards will depend on the types of awards made.
- The types of mechanisms are R21, R01, and P01.
- Eligible organizations include non-profit or for profit organizations.
- Eligible principal investigators include any technically qualified researchers.
- Applicant organizations may submit more than one application.
- Application kits are available from: <http://grants.nih.gov/grants/funding/phs398/phs398.html>

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Section I. Funding Opportunity Description

Purpose:

The purpose of this Request for Applications (RFA) is to solicit applications that will lead to an increased knowledge of membrane protein structures. In contrast to the remarkable advances that have been made in the understanding of soluble proteins, understanding of the structure, function, and mechanisms of integral membrane proteins has been limited by the paucity of available high resolution structures. Applications are requested for the development of innovative methods for production of membrane proteins, production of proteins in sufficient quantities for study, and structural studies of membrane proteins. Novel approaches to cloning, expression, oligomeric assembly, solubilization, stabilization and purification of membrane proteins are needed to advance the production of structurally and functionally intact membrane proteins suitable for structural studies. Innovations are also needed in methods for structure determination, including crystallization, phasing, isotopic labeling, and collection of x-ray crystallographic, nuclear magnetic resonance (NMR), and other relevant data. In addition to methods development projects, applications to obtain preliminary data in support of regular investigator-initiated research projects and to conduct structural studies of integral membrane proteins may be submitted.

Background:

Membrane proteins play a crucial role in many cellular and physiological processes. They are essential mediators of material and information transfer between cells and their environment, between compartments within cells, and between compartments comprising the organ systems. Functionally normal membrane proteins are vital to health, and specific defects are associated with many known disease states. Membrane proteins are the targets of a large number of pharmacologically and toxicologically active substances and are responsible, in part, for their uptake, metabolism, and clearance.

Considerable research is ongoing in the area of membrane protein structure and function, yet relatively few investigators have applied the techniques of x-ray crystallography, electron diffraction, or NMR spectroscopy to study directly the structures of their proteins. During the past decade, approximately 80 unique membrane protein structures have been solved, and each structure has made a major contribution in its area of science. (See http://blanco.biomol.uci.edu/Membrane_Proteins_xtal.html and/or <http://www.mpibp-frankfurt.mpg.de/michel/public/memprotstruct.html>.) This progress clearly demonstrates that obtaining membrane protein structures is feasible. However, during this same decade the rate of soluble protein structure determination has accelerated greatly, and there remains a gap between the understanding of membrane proteins and their soluble protein counterparts (1).

During the past ten years, NIH has stimulated work on membrane protein structures through a series of program announcements (2). This approach has been partially successful and additional NIH funding of this area has resulted. However, certain types of essential technology development and non-hypothesis-driven research have been only modestly supported. Until recently, specific funds have not been set aside for work on membrane proteins. In competition with traditional hypothesis-driven studies of biological mechanisms, applications for novel methods for production of suitable materials for structural studies and exploratory research to obtain preliminary structural data have had only modest success in peer review.

An increase in the number of known membrane protein structures will contribute to an enhanced understanding of many basic phenomena underlying cellular functions essential to human health. To address this and other difficult research problems, the NIH Director, Dr. Elias Zerhouni established the NIH Road Map process for program initiative prioritization (<http://nihroadmap.nih.gov/>). This process identified Structural Biology, especially the determination of membrane protein structures, as a major area for additional investment.

The Structural Biology Road Map process has been critical in creating a specific set-aside of funds dedicated to membrane protein structural studies. As a result, an RFA was issued in FY04 that solicited applications to establish Centers for Innovation in Membrane Protein Production (3). A reasonable number of applications was received, and two Centers will be funded in late FY04. This solicitation is intended to complement these Centers and to encourage novel

investigator-initiated ideas through smaller scale activities such as exploratory studies for high-risk research, regular research projects, and program projects. Furthermore, although production of protein is a key limiting step in the solution of membrane protein structures, it is not the only problematic step. Therefore, this RFA has been broadened to include all activities necessary to produce high-resolution structural models of membrane proteins.

Suggested research topics include, but are not limited to:

- Innovative methods that will yield structurally and functionally intact membrane proteins for subsequent structural studies. Thus far, most membrane protein structures have been solved for proteins that can be obtained from naturally rich sources. However, many of the proteins of greatest human physiological and pharmaceutical relevance are of relatively low abundance. Although membrane proteins may be expressed in recombinant form, there is a need to develop more robust expression systems. For oligomeric membrane proteins, efficient co-expression of membrane protein subunits and assembly systems are required to yield functional, integral membrane proteins and complexes suitable for structural studies.
- Insights into the ways that detergents and lipids interact with membrane proteins. For example, it is not clear why certain detergents and/or lipids with novel phase properties are more successful in the solubilization of membrane proteins than others. Innovations are needed in the chemical synthesis of novel detergents and/or the development of non-detergent methods for solubilizing and stabilizing membrane proteins. Efficient methods are needed to characterize the functional state of the expressed and purified membrane proteins as well as their lipid and detergent contents, state of aggregation, physical homogeneity, and sequence microheterogeneity. Innovative, sensitive mass spectrometric methods are needed to characterize the homogeneity and stoichiometry of membrane protein assemblies, relating functionality to required constituents.
- Innovations in the fractionation and purification of membrane proteins. Novel applications of genomic and proteomic approaches and screens that might complement or enhance traditional approaches such as centrifugation, partitioning, precipitation, chromatography, isoelectric focusing, and electrophoresis are requested. Non-traditional approaches such as the use of protein and/or lipid chaperones, conformation-specific antibodies, covalent modification, stabilizing mutations, and structural scaffolds could be developed to express, solubilize, and purify membrane proteins.
- Innovative methods for x-ray crystallography of membrane proteins. These may include novel apparatus and reagents for membrane protein crystallization as well as efforts to improve the crystallizability of the target protein such as sequence modifications, fusion proteins, antibody complexes, and other co-crystallization aids. Additional innovations are needed to stabilize, freeze, and manipulate often fragile membrane protein crystals for data collection. Given the large size of many membrane proteins and often lower quality diffraction, phasing can be difficult; new approaches are needed here as well. Finally insights gained through analysis of the structures of membrane proteins and their crystallization habits may be useful.
- Developments that would significantly improve the ultimate resolution of single particle electron microscopic and electron diffraction methods applied to 2D and other crystal forms to atomic resolution and improve their general applicability to membrane proteins.
- Innovations in both solid state and solution NMR spectroscopy methods to improve their applicability to larger size membrane proteins. Improvements are needed in isotopic labeling methods and for data collection on limited samples with significant non-protein background signals from detergent and lipids.
- Innovations in other biophysical techniques, such as mass spectrometric methods, that can yield substantially detailed information about overall membrane protein structure leading to models comparable in quality to those of x-ray and NMR methods. Please contact NIH staff to discuss the appropriateness of these areas in response to this RFA.
- Studies designed to advance the determination of the structures of functional protein complexes involving membrane proteins.

In addition to encouraging the development of new methods, this RFA also seeks to support new efforts to accomplish the solution of membrane protein structures at atomic resolution.

Scientific Personnel and Community Development Objectives:

It is expected that many of the projects will be collaborative efforts between chemists, biochemists, molecular biologists, and biophysicists with expertise in the synthesis of probes, novel solubilizing and stabilizing reagents; in cloning and expression; in the isolation and characterization of membrane-bound proteins; and in x-ray crystallography, NMR, and other structural methods. A major aim of this RFA is to stimulate such multidisciplinary collaborations. A further aim is to encourage additional investigators, particularly new investigators, to begin work in this area.

The focus on innovation in protein production and determination of integral membrane protein structures supported by this RFA will complement other efforts underway to understand the structures of all proteins. A major activity in this regard is the Protein Structure Initiative or PSI (4). The PSI Centers are expected to solve large numbers of protein structures in a high-throughput fashion, but membrane proteins are not currently amenable to high throughput efforts. The above mentioned NIH Roadmap Centers for Innovation in Membrane Protein Production are intended to address part of this problem. Another complementary effort is the recently issued RFA that solicits applications to establish Specialized Centers for Protein Structure Initiative (5). These Centers will focus on challenging proteins that are not currently amenable to high throughput and therefore represent major bottlenecks of the structural genomics pipeline. The Specialized Centers are expected to develop methods that will lead to the production and structure determination of significant numbers of these proteins, especially in the later years of the project.

All three types of centers (the PSI centers, the Specialized Centers, and the Centers for Innovation in Membrane Protein Production) include information and material sharing activities. They also have mechanisms for providing access to unique facilities and expertise to the broader scientific community. They are intended to nucleate efforts for the entire field of protein structure. Investigators may wish to contact the center directors to see how their work could interface with the activity of the centers.

Investigators are reminded that in addition to this RFA, NIH also seeks to support research on membrane protein structure through the Structural Biology of Membrane Proteins Program Announcement PA-02-060. See: <http://grants.nih.gov/grants/guide/pa-files/PA-02-060.html>

Eligible small businesses, with or without academic collaborators, may also wish to consider applying for support through the Structural Biology of Membrane Proteins SBIR/STTR Announcement PA-02-108. See: <http://grants.nih.gov/grants/guide/pa-files/PA-02-108.html>

References:

(1) The progress of membrane protein structure determination. Stephen H. White, *Protein Science* (2004), 13:1948–1949.

(2) Structural Biology of Membrane Proteins Program Announcements (PA-95-035, PA-99-004, PA-02-060) and Structural Biology of Membrane Proteins SBIR/STTR Announcement (PA-02-108). See NIH Guide: <http://grants.nih.gov/grants/guide/pa-files/>.

(3) Centers for Innovation in Membrane Protein Production (RFA-RM-04-009). See: <http://grants1.nih.gov/grants/guide/rfa-files/RFA-RM-04-009.html>.

(4) Protein Structure Initiative. See: <http://www.nigms.nih.gov/psi/>.

(5) Specialized Centers for the Protein Structure Initiative (RFA-GM-05-002). See: <http://grants2.nih.gov/grants/guide/rfa-files/RFA-GM-05-002.html>.

Section II. Award Information

1. Mechanism(s) of Support

This funding opportunity will use the Regular Research Project (R01), Exploratory Research (R21), and Program Project (P01) grant award mechanisms. As an applicant, you will be solely responsible for planning, directing, and executing the proposed project. Applicants should consider the type of mechanism appropriate to the scope of the work that they propose. Applicants are encouraged to contact NIH staff to discuss the suitability of their proposal to the R21 or P01 grant mechanisms.

This funding opportunity uses just-in-time concepts. It also uses the modular as well as the non-modular budget formats (see <http://grants.nih.gov/grants/funding/modular/modular.htm>). Specifically, if you are submitting an application with direct costs in each year of \$250,000 or less, use the modular budget format described in the PHS 398 application instructions. Otherwise follow the instructions for non-modular research grant applications.

2. Funds Available

The NIH intends to commit approximately \$5 million total costs in FY2005 to fund applications in response to this RFA. The number of awards will depend on the numbers of R01, R21, and P01 awards that are made. This will depend on the number of applications of each type that are received, their scientific merit as determined by peer review, and award decisions based on the award criteria described below. Regular Research Project (R01) grant awards may be for any amount, but are typically in the range \$100,000 to \$300,000 direct costs per year for a period of three to five years. Program Project (P01) grants typically include several subprojects (minimum of three) and range up to \$1 million direct costs per year for five years. Exploratory Research (R21) grant awards range up to a maximum of \$250,000 direct costs per year for one to two years. The anticipated start date for awards in response to this RFA is September, 2005. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration 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.

Section III. Eligibility Information

1. Eligible Applicants

1.A. Eligible Institutions

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

- For-profit or non-profit
- Public or private institutions, such as universities, colleges, hospitals, and laboratories
- Units of State and local governments
- Eligible agencies of the Federal government
- Domestic (or foreign) institutions/organizations
- Foreign institutions are eligible to apply for R01 and R21 grants
- Faith-based or community-based organizations

All application mechanisms may include consortium arrangements involving foreign institutions, but the parent project must be submitted by a domestic organization. NIH components may be included in subprojects and collaborations, but grant funds cannot be awarded to NIH components or transferred to intramural investigators and laboratories.

1.B. Eligible Individuals

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.

2. Cost Sharing

Cost sharing is not required.

3. Other-Special Eligibility Criteria

None

Section IV. Application and Submission Information

1. Address to Request Application Information

The PHS 398 application instructions are 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.

Telecommunications for the hearing impaired: TTY 301-451-0088.

2. Content and Form of Application Submission

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a D&B Data Universal Numbering System (DUNS) number as the universal identifier when applying for Federal grants or cooperative agreements. The D&B number can be obtained by calling (866) 705-5711 or through the web site at <http://www.dnb.com/>. The D&B number should be entered on line 11 of the face page of the PHS 398 form.

See also Subsection VI.2. Administrative Requirements for additional information.

The title and number of this funding opportunity must be typed on line 2 of the face page of the application form and the YES box must be checked.

3. Submission Dates

3.A. Receipt, Review and Anticipated Start Dates

Letter of Intent Receipt Date: December 23, 2004
Application Receipt Date(s): January 24, 2005
Peer Review Date: June/July, 2005
Council Review Date: September, 2005
Earliest Anticipated Start Date: September, 2005

3.A.1. Letter of Intent

Prospective applicants are asked to submit a letter of intent that includes the following information:

- Descriptive title of proposed research
- Name, address, and telephone number of the Principal Investigator
- Names of other key personnel
- Participating institutions
- Number and title of this funding opportunity

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 IC 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:

John C. Norvell, Ph.D.
Division of Cell Biology and Biophysics
National Institute of General Medical Sciences
Building 45, Room 2AS.13B, MSC 6200
Bethesda, MD 20892-6200
Telephone: (301) 594-0533
FAX: (301) 480-2004
Email: norvellj@nigms.nih.gov

3.B. Sending an Application to the NIH

Applications must be prepared using the PHS 398 research grant application instructions and forms as described above. 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 (U.S. Postal Service Express or regular mail)
Bethesda, MD 20817 (for express/courier service; non-USPS service)

At the time of submission, two additional copies of the application and all copies of the appendix material must be sent to:

Dr. Helen R. Sunshine, Chief
Office of Scientific Review
National Institute of General Medical Sciences
45 Center Drive, MSC 6200
Building 45, Room Number 3AN.12F
Bethesda, MD 20892-6200
Telephone: (301) 594-2881
FAX: (301) 480-8506
Email: sunshinh@nigms.nih.gov

Using the RFA Label: The RFA label available in the PHS 398 application instructions 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/label-bk.pdf>.

3.C. 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.

The NIH 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.

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

4. Intergovernmental Review

This initiative is not subject to [intergovernmental review](#).

5. Funding Restrictions

All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The Grants Policy Statement can be found at <http://grants.nih.gov/grants/policy/policy.htm> (see also Section VI.3. Award Criteria).

6. Other Submission Requirements

Applications requesting up to \$250,000 per year in direct costs must be submitted in a modular budget format. The modular budget format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in \$25,000 modules. Section C of the research grant application instructions for the PHS 398 (rev. 5/2001) at <http://grants.nih.gov/grants/funding/phs398/phs398.html> includes step-by-step guidance for preparing modular budgets. Additional information on modular budgets is available at <http://grants.nih.gov/grants/funding/modular/modular.htm>.

Plan for Sharing Research Data

The precise content of the data-sharing plan will vary, depending on the data being collected and how the investigator is planning to share the data. Applicants who are planning to share data may wish to describe briefly the expected schedule for data sharing; the format of the final dataset; the documentation to be provided; whether or not any analytic tools also will be provided; whether or not a data-sharing agreement will be required and, if so, a brief description of such an

agreement (including the criteria for deciding who can receive the data and whether or not any conditions will be placed on their use); and the mode of data sharing (e.g., under their own auspices by mailing a disk or posting data on their institutional or personal website, through a data archive or enclave). Investigators choosing to share under their own auspices may wish to enter into a data-sharing agreement. Applicants are encouraged to consider depositing data into databases that evolve as activities of the Centers for Innovation in Membrane Protein Production and Specialized Centers for the Protein Structure Initiative. All applicants must include a **plan** for sharing research data in their application. The data sharing policy is available at http://grants.nih.gov/grants/policy/data_sharing. All investigators responding to this funding opportunity should include a description of how final research data will be shared, or explain why data sharing is not possible. References to data sharing may also be appropriate in other sections of the application.

The reasonableness of the data sharing **plan** or the rationale for not sharing research data will be assessed by the reviewers. However, reviewers will not factor the proposed data sharing **plan** into the determination of scientific merit or the priority score.

Sharing Research Resources

NIH policy requires that grant awardee recipients make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication (NIH Grants Policy Statement <http://grants.nih.gov/grants/policy/nihgps> and http://ott.od.nih.gov/newpages/rtguide_final.html). Investigators responding to this funding opportunity should include a **plan** for sharing research resources addressing how unique research resources will be shared or explain why sharing is not possible.

The adequacy of the data sharing **plan** and the resources sharing **plan** will be considered by Program staff of the funding organization when making recommendations about funding applications. The effectiveness of the resource sharing will be evaluated as part of the administrative review of each non-competing Grant Progress Report (PHS 2590). See Section VI.3. Award Criteria.

Participation in Annual Meetings

Applicants are encouraged to plan for participation in annual meetings of the community researchers pursuing membrane protein structures through Roadmap funded initiatives. Funds to support the required travel should be requested.

Section V. Application Review Information

1. Criteria

See review and award criteria below.

2. Review and Selection Process

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by NIGMS. Incomplete applications will not be reviewed.

As part of the initial merit review, all applications will:

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

3. Merit Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, to improve the control of disease, and to enhance health. In their written critiques, reviewers will be asked to comment on each of the following criteria 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 addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that an 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.

1. Significance. Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or clinical practice be advanced? What will be the effect of these studies on the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

2. Approach. Are the conceptual or clinical framework, design, methods, and analyses adequately developed, well integrated, well reasoned, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

3. Innovation. Is the project original and innovative? For example: Does the project challenge existing paradigms or clinical practice; address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area?

4. Investigators. Are the investigators 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? Does the investigative team bring complementary and integrated expertise to the project (if applicable)?

5. Environment. Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements? Is there evidence of institutional support?

3.A. 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:

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 the Research Plan, Section E on Human Subjects in the PHS Form 398).

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 will be assessed. Plans for the recruitment and retention of subjects will also be evaluated (see the Research Plan, Section E on Human Subjects in the PHS Form 398).

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 Form 398 research grant application instructions will be assessed.

3.B. Additional Review Considerations

Budget: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research. The priority score should not be affected by the evaluation of the budget.

3.C. Sharing Research Data

Data Sharing Plan: The reasonableness of the data sharing **plan** or the rationale for not sharing research data **will** be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or the priority score. The presence of a data sharing **plan** will be part of the terms and conditions of the award. The funding organization will be responsible for monitoring the data sharing policy.

3.D. Sharing Research Resources

NIH policy requires that grant awardee recipients make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication. NIH Grants Policy Statement <http://grants.nih.gov/grants/policy/nihgps> and http://ott.od.nih.gov/newpages/rtguide_final.html. Investigators responding to

this funding opportunity should include a sharing research resources **plan** addressing how unique research resources will be shared or explain why sharing is not possible

The adequacy of the resources sharing **plan** will be considered by Program staff of the funding organization when making recommendations about funding applications. Program staff may negotiate modifications of the data and resource sharing **plans** with the Principal Investigator before recommending funding of an application. The final version of the data and resource sharing **plans** negotiated by both will become a condition of the award of the grant. The effectiveness of the resource sharing will be evaluated as part of the administrative review of each non-competing Grant Progress Report (PHS 2590). See Section VI.3. Award Criteria.

Section VI. Award Administration Information

1. Award Notices

After the peer review of the application is completed, the Principal Investigator will also receive a written critique called a summary statement.

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant. For details, applicants may refer to the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part4.htm

Once final funding decisions are made, a formal notification in the form of a Notice of Grant Award will be provided to the applicant organization. The Notice of Grant Award signed by the grants management officer is the authorizing document.

Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NGA (Notice of Grant Award) are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs.

The Notice of Grant Award will be sent by Email to the organizational business official indicated on the face page of the application.

2. Administrative Requirements

All NIH grant and cooperative agreement awards include the NIH Grants Policy Statement as part of the notice of grant award. For these terms of award, see the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part4.htm) and Part II Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part9.htm).

3. Award Criteria

The following will be considered in making funding decisions:

- Scientific merit of the proposed project as determined by peer review
- Availability of funds
- Relevance of program priorities

4. Reporting

Awardees will be required to submit the PHS Non-Competing Grant Progress Report, Form 2590 annually (<http://grants.nih.gov/grants/funding/2590/2590.htm>) and financial statements as required in the NIH Grants Policy Statement.

5. Program Evaluation

NIH plans to assess Roadmap related activities in the future and may independently of this announcement contact awardees regarding the activities conducted under awards made under this RFA.

Section VII. Agency Contacts

We encourage your inquiries concerning this funding opportunity 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:

1. Scientific/Research Contacts:

John C. Norvell, Ph.D.
Division of Cell Biology and Biophysics
National Institute of General Medical Sciences
Building 45, Room 2AS.13B, MSC 6200
Bethesda, MD 20892-6200
Telephone: (301) 594-0533
FAX: (301) 480-2004
Email: norvellj@nigms.nih.gov

2. Peer Review Contacts:

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Office of Scientific Review
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Section VIII. Other Information

Required Federal Citations

Use of Animals in Research:

Recipients of PHS support for activated involving live, vertebrate animals must comply with PHS Policy on Humane Care and Use of Laboratory Animals (<http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf>), as mandated by the Health Research Extension Act of 1985 (<http://grants.nih.gov/grants/olaw/references/hrea1985.htm>), and the USDA Animal Welfare Regulations (<http://www.nal.usda.gov/awic/legislat/usdaleg1.htm>), as applicable.

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://www.hhs.gov/ohrp/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). Monitoring should be commensurate with risk. The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risks 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:

Investigators submitting an NIH application seeking \$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. Reviewers will consider the data sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

Sharing of Model Organisms:

NIH is committed to support efforts that encourage sharing of important research resources including the sharing of model organisms for biomedical research (see <http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html>). At the same time the NIH recognizes the rights of grantees and contractors to elect and retain title to subject inventions developed with Federal funding pursuant to the Bayh Dole Act (see the NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm). All investigators submitting an NIH application or contract proposal beginning with the October 1, 2004 receipt date, are expected to include in the application/proposal a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding or state why such sharing is restricted or not possible. This will permit other researchers to benefit from the resources developed with public funding. The inclusion of a model organism sharing plan is not subject to a cost threshold in any year and is expected to be included in all applications where the development of model organisms is anticipated.

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 (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html>); a complete copy of the updated Guidelines is 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 Clinical Research:

The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.

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 and individuals designated as key personnel. The policy is available 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).

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 proposals 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 PA 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.

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