

PATHOGENESIS AND TREATMENT OF LYMPHEDEMA AND LYMPHATIC DISEASES

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Department of Health and Human Services (DHHS)

PARTICIPATING ORGANIZATION:

National Institutes of Health (NIH)

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

COMPONENTS OF PARTICIPATING ORGANIZATION:

National Heart, Lung, and Blood Institute (NHLBI)

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

National Institute of Child Health and Human Development (NICHD)

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

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

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

National Cancer Institute (NCI)

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

National Center for Complementary and Alternative Medicine (NCCAM)

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

National Institute on Biomedical Imaging and Bioengineering (NIBIB)

(<http://www.nibib1.nih.gov/>)

National Institute of Nursing Research (NINR)

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

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PURPOSE OF THIS PA

The National Heart, Lung, and Blood Institute (NHLBI), National Institute of Child Health and Human Development (NICHD), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Cancer Institute (NCI), National Institute of Nursing Research (NINR), National Center for Complementary and Alternative Medicine (NCCAM), and National Institute on Biomedical Imaging and Bioengineering (NIBIB) invite qualified researchers to submit applications for research project grants to investigate the pathogenesis and new treatments for primary and secondary lymphedema. The purpose of this program announcement is to stimulate research on the biology of the lymphatic system, to characterize at the molecular, cellular, tissue, organ, and intact organism levels, the pathophysiologic mechanisms that cause the disease, to develop new methods for quantitating and imaging lymph flow, to discover new therapeutic interventions, and to determine the safety, efficacy and mechanisms of action of complementary and alternative therapies. The scope of this research includes developmental biology and genetics of the lymphatic system to identify and characterize genes important for its organization and regulation. Such knowledge will help to improve early diagnosis of affected individuals, the choice and timing of treatment, and genetic counseling. Research is also needed on the pathophysiology of the disorders of skin and subcutaneous tissue secondary to chronic lymphedema, and lymphedema which results from cancers and cancer treatment, with an ultimate goal to develop more targeted and effective therapies.

RESEARCH OBJECTIVES

The lymphatic system comprises an important secondary circulatory system, returning interstitial fluid back to the venous circulation. Prior to this function, lymphatic vessels also regulate accumulation and turnover of interstitial fluid. When the mechanisms involved with this regulation become unbalanced, lymphedema results. There are two major types of lymphedema: primary (congenital) and secondary (caused by tissue injury, scarring, lymph node removal, or infection). For primary lymphedema, there is an early onset form (Milroy's disease) which is relatively rare and presents at birth. A more common type (Meige's disease) develops during puberty, representing approximately 80 percent of all cases. A third form, lymphedema tarda, occurs after the age of 35. Lymphedema frequently presents with one leg being more swollen than the other, which is not only disfiguring, but can lead to a severe infection (cellulitis), and diseases of the skin and subcutaneous tissues. Primary lymphedema is inherited in an autosomal dominant fashion, with variable expressivity and penetrance, and with women affected almost three-fold more often than men. The complexity of lymphatic development and function is likely to be regulated by a variety of unidentified genes, which result in the phenotype secondary to mutations in those genes. Gene defects have been mapped in several families, with a recent study showing that a form of primary lymphedema

involves a genetic missense mutation located on chromosome 5 for the receptor for vascular endothelial growth factor-C. This genetic lesion may implicate specific tyrosine kinase receptors as causative in certain types of lymphedema. However, the exact mechanisms which contribute to primary lymphedema remain unknown.

The incidence of primary lymphedema has been estimated to be between 1/6000 to 1/300 live births. Thus, it could be a rare disease, or a more common disease which is underrecognized. On the other hand, there are 3-5 million people affected with secondary lymphedema in the United States, and according to the World Health Organization as many as 170 million world-wide. The secondary type of lymphedema develops after tissue injury, especially after cancer surgery, radiation therapy, trauma to the lymphatic system and lymphangitis, inflammation or infection (e.g. filariasis) that interrupts normal lymphatic pathway function.

Although lymphedema has been recognized for over a century, understanding its causes has received limited attention. The etiology of the disease is believed to be complex, involving defective fluid and solute transport across lymphatic vessels, insufficient propulsion of lymph within lymphatic vessels, and developmental defects unique to the lymphatic system. Further, therapy also has lagged, despite the prevalence of the disease, and little relief is gained from current interventions. One important factor responsible for the lack of study and treatment of lymphedemas is the paucity of unique animal models, including transgenic and knockout models, compared to other diseases.

In view of the limited attention currently given to the biology of the lymphatic system, and the treatment of lymphedema, the NHLBI, NICHD, NIAMS, NCI, NINR, NIBIB, and NCCAM are interested in approaches that will identify the developmental, molecular, and cellular defects that contribute to lymphedema as well as the development of effective therapeutic interventions to treat both primary and secondary lymphedemas. These include: insufficiency of lymphatic circulatory function; lymphatic vascular valvular insufficiencies; complex congenital vascular proliferative diseases of the lymphatic vasculature, including but not limited to, so-called lymphangioma, cystic hygroma, lymphangiosarcoma, lymphangio-leiomyomatosis; and developmental disorders of the lymphatic system, e.g. lymphangiectasia, chylous reflux and complex vascular malformations, such as Klippel-Trenauny Syndrome.

Examples of some research topics are listed below to illustrate the objectives of this program announcement. It is not required that all or any of these ideas be included; investigators are encouraged to submit applications that are relevant to the goals of this program announcement.

1. Comparative studies of gene expression in lymphedematous and normal tissues, using techniques such as laser capture microdissection and high density microarrays to identify molecular targets.
2. Studies on the phenotypic and genotypic differences of lymphatic vascular cells, compared to arterial and venous vascular cells.

3. Elucidation of the process of lymphangiogenesis, including the growth factors, cytokines, and matrix molecules associated with the formation of functional lymphatic vessels. A potential role of trophism to lymph nodes, and the effect of reimplantation of nodal tissue on lymphedema.
4. Development of a biophysical model(s) for interstitial fluid exchange across the lymphatic wall, and the role of the lymphatic matrix in the development of lymphedema. Characterization of the physical and biological mechanisms in the propulsion of lymph within lymphatic vessels.
5. The creation of animal models to confirm the identification of putative genes contributing to lymphedema, and the development of animal models to assess new and complementary or alternative treatments.
6. The development of methods to image and quantitate lymph flow to provide useful endpoints for clinical evaluations.
7. Approaches to explain the asymmetry between more and less affected limbs in an individual with primary lymphedema, when the genetics and environment appear to be uniform. Also, the developmental or hormonal basis for onset that occurs during puberty.
8. Studies on the developmental biology and developmental genetics of the lymphatic system, i.e., the identification and characterization of genes important in the organization and regulation of the development of the lymphatic system.
9. Studies on diseases of skin and subcutaneous tissue that result from chronic lymphedema.
10. New methods to prevent or treat lymphedema or lessen its impact on patients.
11. Development of biobehavioral markers to measure the relationship between health-related quality of life (HRQOL) and lymphedema, including markers to measure the impact of therapeutic interventions.
12. A national patient registry and tissue bank.

To foster data sharing in addition to presentations and publications, investigators should consider how to make experimental results available to other scientists for data mining, and how to make archived data interoperable with commercially available software.

MECHANISM(S) OF SUPPORT

This PA will use the NIH individual research project grant (R01) award mechanism. As an applicant, you will be solely responsible for planning, directing, and executing the proposed project, which is not to exceed a period of 5 years. This PA also uses just-in-

time concepts, and the modular budgeting as well as the non-modular budgeting 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. Otherwise follow the instructions for non-modular budget research grant applications. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm.

ELIGIBLE INSTITUTIONS

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

- o For-profit or non-profit organizations
- o Public or private institutions, such as universities, colleges, hospitals, and laboratories
- o Units of State and local governments
- o Eligible agencies of the Federal government
- o Domestic or foreign institutions/organizations
- o Faith-based or community-based organizations

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

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

SPECIAL REQUIREMENTS

For clinical studies, a Data and Safety Monitoring Plan (e.g. creation of a Data Safety and Monitoring Board, refer to Federal Citation at the end of the document); documented ability to enroll a specified number of patients; semi-annual reports; special expertise or facilities; review between Phase I and Phase II; and coordination among investigators (e.g. annual meetings), etc., must be included.

Describe any requirements for sharing research data, if appropriate. Note that all applications that list direct costs greater than \$500,000 in any year of the proposed research, must have a data sharing plan.

WHERE TO SEND INQUIRIES

We encourage your inquiries concerning this PA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into two areas: scientific/research and financial or grants management issues:

- o Direct your questions about scientific/research issues to:

Henry Chang, M.D.
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute
6701 Rockledge Drive, MSC 7950
Bethesda, MD 20892-7950
Telephone: (301) 435-0067
FAX: (301) 480-1060
Email: changh@nih.gov

Stephen S. Goldman, Ph.D.
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
6701 Rockledge Drive, MSC 7956
Bethesda, MD 20892-7956
Telephone: (301) 435-0565
FAX: (301) 480-2849
Email: goldmans@nih.gov

A. Tyl Hewitt, Ph.D.
Chief, Developmental Biology, Genetics and Teratology Branch
National Institute of Child Health and Human Development
Building 6100, Room 4B01E
6100 Executive Blvd. MSC 7510
Bethesda MD 20892-7510
Telephone: (301) 496-5541
FAX: (301) 480-0303
Email: th119v@nih.gov

Alan N. Moshell, M.D.
Skin Diseases Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Building 45, Room 5AS25L
45 Center Drive, MSC 6500
Bethesda, MD 20892-6500
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FAX: (301) 480-4543
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Suresh Mohla, Ph.D.
Chief, Tumor Biology & Metastasis Branch
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National Cancer Institute
6130 Executive Blvd, EPN 5038
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FAX: 301 480-0864
Email: mohlas@mail.nih.gov

Martha L. Hare, Ph.D., R.N
National Institute of Nursing Research
6701 Democracy Boulevard
One Democracy Plaza, Room 710
Bethesda, MD 20892-4870 (Courier: 20817)
Phone: 301-451-3874
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Email: martha.hare@nih.gov

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Alan C. McLaughlin, Ph.D.
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Bethesda, MD 20892-5477
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FAX: (301) 480-4973
Email: mclaugal@mail.nih.gov

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

Suzanne White
Grants Operations Branch
National Heart, Lung, and Blood Institute
Rockledge 2, Room 7160
Bethesda, MD 20892-7926
Telephone: (301) 435-0171
FAX: (301) 480-3310
Email: WhiteSa@nhlbi.nih.gov

Annette Hanopole
Grants Management Branch
National Institute of Child Health and Human Development
Bldg. 6100, Room 8A17F
6100 Executive Blvd. MSC 7510

Bethesda, MD 20892-7510
Telephone: (301) 435-6975
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45 Center Drive, MSC 6500
Bethesda, MD 20892-6500
Telephone: (301) 594-3535
FAX: (301) 480-5450
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Mr. Bill Wells
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National Cancer Institute
Executive Plaza South 243
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Email: curlingn@mail.nih.gov

SUBMITTING AN APPLICATION

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

The title and number of this program announcement must be type on line 2 of the face page of the application form and the YES box must be checked.

APPLICATION RECEIPT DATES: Applications submitted in response to this program announcement will be accepted at the standard application deadlines, which are available at <http://grants.nih.gov/grants/dates.htm>. Application deadlines are also indicated in the PHS 398 application kit.

SPECIFIC INSTRUCTIONS FOR MODULAR BUDGET GRANT APPLICATIONS: Applications requesting up to \$250,000 per year in direct costs must be submitted in a modular budget grant format. The modular budget grant 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 grants. Additional information on modular grants is available at <http://grants.nih.gov/grants/funding/modular/modular.htm>.

SPECIFIC INSTRUCTIONS FOR APPLICATIONS REQUESTING \$500,000 OR MORE PER YEAR: Applications requesting \$500,000 or more in direct costs for any year must include a cover letter identifying the NIH staff member within one of NIH institutes or centers who has agreed to accept assignment of the application. Applicants requesting more than \$500,000 must carry out the following steps:

- 1) Contact the IC program staff at least 6 weeks before submitting the application, i.e., as you are developing plans for the study;

2) Obtain agreement from the IC staff that the IC will accept your application for consideration for award; and,

3) Identify, in a cover letter sent with the application, the staff member and IC who agreed to accept assignment of the application.

This policy applies to all investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended or revised version of these grant application types. Additional information on this policy is available in the NIH Guide for Grants and Contracts, October 19, 2001 at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-004.html>.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the checklist, and five 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)

APPLICATION PROCESSING: Applications must be mailed on or before the receipt dates described at <http://grants.nih.gov/grants/funding/submissionschedule.htm>. The CSR will not accept any application in response to this PA that is essentially the same as one currently pending initial review unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of a substantial revision of an unfunded version of an application already reviewed, but such application must include an Introduction addressing the previous critique.

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

PEER REVIEW PROCESS

Applications submitted for this PA will be assigned on the basis of established PHS referral guidelines. Appropriate scientific review groups convened in accordance with the standard NIH peer review procedures (<http://www.csr.nih.gov/refrev.htm>) will evaluate applications for scientific and technical merit. As part of initial merit review, all applications will:

- o 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

- o Receive a written critique
- o Receive a second level review by the appropriate national advisory council or board

REVIEW CRITERIA

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

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

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

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

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

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

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

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

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations, below). <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>

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 Inclusion Criteria in the sections on Federal Citations, below).

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

ADDITIONAL REVIEW CONSIDERATIONS

Sharing Research Data

Applicants requesting more than \$500,000 in direct costs in any year of the proposed research are expected to include a data sharing plan in their 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 priority score. The policy is at: http://grants.nih.gov/grants/policy/data_sharing/

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

AWARD CRITERIA

Applications submitted in response to a PA will compete for available funds with all other recommended applications. The following will be considered in making funding decisions:

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

REQUIRED FEDERAL CITATIONS

ANIMAL WELFARE PROTECTION: Recipients of PHS support for activities 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://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>

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

SHARING RESEARCH DATA: Starting with the October 1, 2003 receipt date, investigators submitting an NIH application seeking \$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.

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

All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html>); a complete copy of the updated Guidelines are available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III

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

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at <http://grants.nih.gov/grants/funding/children/children.htm>.

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS: NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. You will find this policy announcement in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html>.

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

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

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

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

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

URLS IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and 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.healthypeople.gov/>.

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