

This Program Announcement expires on December 31, 2003, unless reissued.

PATHOGENESIS AND TREATMENT OF LYMPHEDEMA

Release Date: December 14, 2000

PA NUMBER: PA-01-035

National Heart, Lung, and Blood Institute

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

National Institute of Child Health and Human Development

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

National Institute of Arthritis and Musculoskeletal and Skin Diseases

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

National Cancer Institute

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

THIS PA USES THE "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. IT INCLUDES DETAILED MODIFICATIONS TO STANDARD APPLICATION INSTRUCTIONS THAT MUST BE USED WHEN PREPARING APPLICATIONS IN RESPONSE TO THIS PA.

PURPOSE

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), and the National Cancer Institute (NCI) 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, and to characterize at the molecular, cellular, tissue, organ, and intact organism levels, the pathophysiologic mechanisms that cause the disease, and to discover new therapeutic interventions. 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.

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 Program Announcement (PA), "Pathogenesis and Treatment of Lymphedema" 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/>.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit and 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.

MECHANISM OF SUPPORT

This PA will use the National Institutes of Health (NIH) individual research project grant (R01) award mechanism. The applicant will be solely responsible for the planning, direction, and execution of the proposed project, which is not to exceed a period of 5 years. Specific application instructions have been modified to reflect "MODULAR GRANT" and "JUST-IN-TIME" streamlining efforts being examined by the NIH. Complete and detailed instructions and information on Modular Grant applications can be found at <http://grants.nih.gov/grants/funding/modular/modular.htm>.

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, and NCI 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. 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 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 delayed onset 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. Methods to prevent radiation-induced or surgery-related lymphedema

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.

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 biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification are 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 research involving human subjects should read the UPDATED "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research," published in the NIH Guide for Grants and Contracts on August 2, 2000 (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html>); a complete copy of the updated Guidelines are available at http://grants.nih.gov/grants/funding/women_min/guidelines_update.htm. The revisions relate to NIH defined Phase III clinical trials and require: a) all applications or proposals and/or protocols to 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) all investigators to report accrual, and to conduct and report 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.

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

APPLICATION PROCEDURES

Applications are to be submitted on the grant application form PHS 398 (rev.4/98) and will be accepted at the standard application deadlines as indicated in the application kit. Application kits are available at most institutional offices of sponsored research and may be obtained from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435- 0714, email: GrantsInfo@nih.gov.

Applicants planning to submit an investigator-initiated 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 are advised that he or she must contact the Institute or Center (IC) program staff before submitting the application, i.e, as plans for the study are being developed. Furthermore, the application must obtain agreement from the IC staff that the IC will accept the application for consideration for award. Finally, the applicant must identify, in a cover letter sent with the application, the staff member and Institute or Center who agreed to accept assignment of the application.

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, March 20, 1998 at <http://grants.nih.gov/grants/guide/notice-files/not98-030.html>

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS

The modular grant concept establishes specific modules in which direct costs may be requested as well as a maximum level for requested budgets. Only limited budgetary information is required under this approach. The just-in-time concept allows applicants to submit certain information only when there is a possibility for an award. It is anticipated that these changes will reduce the administrative burden for the applicants, reviewers and Institute staff. The research grant

application form PHS 398 (rev. 4/98) is to be used in applying for these grants, with the modifications noted below.

Modular Grant applications will request direct costs in \$25,000 modules, up to a total direct cost request of \$250,000 per year. (Applications that request more than \$250,000 direct costs in any year must follow the traditional PHS 398 application instructions.) The total direct costs must be requested in accordance with the program guidelines and the modifications made to the standard PHS 398 application instructions described below:

PHS 398

- o FACE PAGE: Items 7a and 7b should be completed, indicating Direct Costs (in \$25,000 increments up to a maximum of \$250,000) and Total Costs [Modular Total Direct plus Facilities and Administrative (F&A) costs] for the initial budget period. Items 8a and 8b should be completed indicating the Direct and Total Costs for the entire proposed period of support.

- o DETAILED BUDGET FOR THE INITIAL BUDGET PERIOD - Do not complete Form Page 4 of the PHS 398. It is not required and will not be accepted with the application.

- o BUDGET FOR THE ENTIRE PROPOSED PERIOD OF SUPPORT - Do not complete the categorical budget table on Form Page 5 of the PHS 398. It is not required and will not be accepted with the application.

- o NARRATIVE BUDGET JUSTIFICATION - Prepare a Modular Grant Budget Narrative page. (See <http://grants.nih.gov/grants/funding/modular/modular.htm> for sample pages.) At the top of the page, enter the total direct costs requested for each year. This is not a Form page.

- o Under Personnel, list all project personnel, including their names, percent of effort, and roles on the project. No individual salary information should be provided. However, the applicant should use the NIH appropriation language salary cap and the NIH policy for graduate student compensation in developing the budget request.

For Consortium/Contractual costs, provide an estimate of total costs (direct plus facilities and administrative) for each year, each rounded to the nearest \$1,000. List the individuals/organizations with whom consortium or contractual arrangements have been made, the percent effort of all personnel, and the role on the project. Indicate whether the collaborating institution is foreign or domestic. The total cost for a consortium/contractual arrangement is

included in the overall requested modular direct cost amount. Include the Letter of Intent to establish a consortium.

Provide an additional narrative budget justification for any variation in the number of modules requested.

o BIOGRAPHICAL SKETCH - The Biographical Sketch provides information used by reviewers in the assessment of each individual's qualifications for a specific role in the proposed project, as well as to evaluate the overall qualifications of the research team. A biographical sketch is required for all key personnel, following the instructions below. No more than three pages may be used for each person. A sample biographical sketch may be viewed at:

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

- Complete the educational block at the top of the form page;
- List position(s) and any honors;
- Provide information, including overall goals and responsibilities, on research projects ongoing or completed during the last three years.
- List selected peer-reviewed publications, with full citations;

o CHECKLIST - This page should be completed and submitted with the application. If the F&A rate agreement has been established, indicate the type of agreement and the date. All appropriate exclusions must be applied in the calculation of the F&A costs for the initial budget period and all future budget years.

o The applicant should provide the name and phone number of the individual to contact concerning fiscal and administrative issues if additional information is necessary following the initial review.

The title and number of the program announcement 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 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)

REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established PHS referral guidelines. Applications will be evaluated for scientific and technical merit by an appropriate scientific review group convened in accordance with the standard NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed, assigned a priority score, and 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 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 addressed and 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. 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 be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

(2) 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?

(3) Innovation: Does the project employ novel concepts, approaches or method? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

(4) 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)?

(5) 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?

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

- o The adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

- o The reasonableness of the proposed budget and duration in relation to the proposed research

- o The adequacy of the proposed protection for humans, 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. The following will be considered in making funding decisions: Quality of the proposed project as determined by peer review, availability of funds, and program priority.

INQUIRIES

Inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome. Direct inquiries regarding programmatic issues to:

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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance (<http://www.cfda.gov/public/allprogs.asp>) Nos. 93.837 and 93.839 (NHLBI), 93.865 (NICHD), 93.846 (NIAMS), and 93.396 (NCI). 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.

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