

GENE THERAPY IN DUCHENNE MUSCULAR DYSTROPHY

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PURPOSE

The National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) encourage the submission of research grant applications to investigate the potential for gene therapy in Duchenne muscular dystrophy. Responses to this program announcement may include studies in appropriate animal models of gene replacement using viral vectors, myoblast transfer, or other means of dystrophin enhancement.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention goals of "Healthy People 2000," a PHS-led national activity for setting priorities. This program announcement, Gene Therapy in Duchenne Muscular Dystrophy, is related to the priority area chronic disabling conditions. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: No. 017-001-00474-0, or Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-783-3238).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State or local governments, and eligible agencies of the Federal government. Foreign institutions are eligible to apply for only regular research project grants (R01). Applications from minority individuals and women are encouraged.

MECHANISMS OF SUPPORT

The support mechanisms for grants in this area will be the investigator-initiated research project grant (R01), the First Independent Research Support and Transition (FIRST) award (R29), the program project grant (P01), and the center grant (P50). The Principal Investigator or program director, as well as any participating investigators, will plan, direct, and perform the research. Applicants for program project grants are requested to contact the NINDS representative listed below as early as possible in the planning stages.

RESEARCH OBJECTIVES

Duchenne muscular dystrophy (DMD) is the most common inherited neuromuscular disease, affecting approximately one in 3,500 male births. The disease is characterized by muscle necrosis and regeneration. Eventually, the regeneration cannot keep up with the necrosis, resulting in progressive muscle fiber loss. Affected boys are usually wheelchair-bound by age 12, with death occurring in the third decade. A milder variant, Becker muscular dystrophy, occurs once in 30,000 male births. Isolation of the X-linked DMD gene led to the discovery of dystrophin, the protein that is missing or defective in Duchenne muscular dystrophy and abnormal in Becker muscular dystrophy. Dystrophin is a 427-kd protein and an essential component of the inner surface of the sarcolemmal membrane. The full-length gene for dystrophin is huge, 2.4 megabases, and most mutations are frame-shift deletions (Duchenne) or internal in-frame deletions (Becker).

The most frequently studied animal model of Duchenne muscular dystrophy is the mdx mouse, in which the homologous mutation also results in a lack of dystrophin. Like affected humans, the mdx mice have recurrent muscle fiber necrosis; regeneration, however, is very efficient, and the mice do not suffer generalized muscle fiber loss and weakness. A dog model with a similar mutation may be a superior model of DMD because its size and symptoms are much closer to humans.

Unfortunately, the dog model has several disadvantages compared to the mouse, including slow breeding rate, scarcity, and expense.

Among the potential genetic therapy approaches to dystrophin replacement that have been considered are direct injection of DNA, vector-mediated delivery, and myoblast transfer. These approaches all present major obstacles that must be overcome.

The full-length dystrophin gene with its associated promoters and other regulatory elements may be too large to routinely introduce into muscle fibers directly or using a viral vector. Human cDNA, length about 14 kb, has been isolated, and a partial cDNA of only 6.3 kb has been cloned from a patient with only very mild symptoms, suggesting that such a smaller "minigene" could protect DMD muscles from necrosis. A gene of this size could be accommodated in an adenovirus or retrovirus vector.

Myoblast transfer studies in mice have been reported, with the percentage dystrophin positive host muscle fibers varying widely. Several groups of investigators have also performed similar experiments in Duchenne muscular dystrophy boys. The procedure appears to be safe, but so far there is little evidence of increased strength or the production of dystrophin in the host muscle.

This announcement solicits applications for any study whose ultimate goal is the successful genetic therapy of Duchenne muscular dystrophy. Examples are given below, but applications are not limited to these areas of research:

- o Improve methods to express dystrophin cDNAs in viral vectors, including adenovirus and retrovirus.
- o Develop techniques to increase the penetration of gene constructs into the muscle cells and their nuclei and to enhance the dispersion of injected gene constructs or myoblasts.
- o Develop strategies to enhance the efficiency of myoblast transfer therapy.
- o Investigate the feasibility of the 6.3 kb cDNA for genetic therapy.
- o Find alternative mechanisms to increase levels of existing dystrophin.
- o Assess the feasibility of injecting DNA directly into muscle cells.

STUDY POPULATIONS

SPECIAL INSTRUCTIONS TO APPLICANTS REGARDING IMPLEMENTATION OF NIH POLICIES CONCERNING INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH STUDY POPULATIONS

NIH policy is that applicants for NIH clinical research grants and cooperative agreements will be required to include minorities and women in study populations so that research findings can be of benefit to all persons at risk of the disease, disorder or condition under study; special emphasis must be placed on the need for inclusion of minorities and women in studies of diseases, disorders and conditions which disproportionately affect them. This policy is intended to apply to males and females of all ages. If women or minorities are excluded or inadequately represented in clinical research, particularly in proposed population-based studies, a clear compelling rationale must be provided.

The composition of the proposed study population must be described in terms of gender and racial/ethnic group. In addition, gender and racial/ethnic issues should be addressed in developing a research design and sample size appropriate for the scientific objectives of the study. This information must be included in the form PHS 398 in Sections 1-4 of the research plan AND summarized in Section 5, Human Subjects. Applicants are urged to assess carefully the feasibility of including the broadest possible representation of minority groups. However, NIH recognizes that it may not be feasible or appropriate in all research projects to include representation of the full array of United States racial/ethnic minority populations (i.e., Native Americans (including American Indians or Alaskan Natives), Asian/Pacific Islanders, Blacks, Hispanics). The rationale for studies on single minority population groups must be provided.

For the purpose of this policy, clinical research is defined as human biomedical and behavioral studies of etiology, epidemiology, prevention (and preventive strategies), diagnosis, or treatment of diseases, disorders or conditions, including but not limited to clinical trials.

The usual NIH policies concerning research on human subjects also apply. Basic research or clinical studies in which human tissues cannot be identified or linked to individuals are excluded. However, every effort should be made to include human tissues from women and racial/ethnic minorities when it is important to apply the results of the study broadly, and this should be addressed by applicants. For foreign awards, the policy on inclusion of women applies fully; since the definition of minority differs in other countries, the applicant must discuss the relevance of research involving foreign population groups to the United States' populations, including

minorities. If the required information is not contained within the application, the review will be deferred until the information is provided.

Peer reviewers will address specifically whether the research plan in the application conforms to these policies. If the representation of women or minorities in a study design is inadequate to answer the scientific question(s) addressed and the justification for the selected study population is inadequate, it will be considered a scientific weakness or deficiency in the study design and will be reflected in assigning the priority score to the application.

All applications for clinical research submitted to NIH are required to address these policies. NIH funding components will not award grants or cooperative agreements that do not comply with these policies.

APPLICATION PROCEDURES

Applications are to be submitted on the grant application form PHS 398 (rev. 9/91) according to instructions contained in the application kit. Application kits are available from most institutional offices of sponsored research and may be obtained from the Office of Grants Information, Division of Research Grants, National Institutes of Health, Westwood Building, Room 449, Bethesda, MD 20892, telephone 301-435-0714.

Check "YES" in item 2a on the face sheet of the application and type "Gene Therapy in Duchenne Muscular Dystrophy."

FIRST (R29) applications must include at least three sealed letters of reference attached to the face page of the original application. FIRST applications submitted without the required number of reference letters will be considered incomplete and will be returned without review.

Applicants for the P01 or P50 should use the application format as described in the NINDS pamphlet, NINDS GUIDELINES: PROGRAM PROJECT AND RESEARCH CENTER GRANTS (rev. June 1992). Deadlines for the receipt of applications are February 1, June 1, and October 1. The completed original application and five exact copies must be sent or delivered to:

Division of Research Grants
National Institutes of Health
Westwood Building, Room 240
Bethesda, MD 20892**

If the application is for a program project or center grant, submit the original and three copies to the Division of Research Grants. An additional two copies must be sent to Dr. Nichols at the address listed under INQUIRIES to expedite processing applications for multidisciplinary efforts.

REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established PHS referral guidelines. Applications will be judged on scientific merit and program relevance in accordance with NIH policy and procedures involving peer review. An initial review will be made by an appropriate study section of the Division of Research Grants for regular research grants and FIRST awards, and by an appropriate institute committee for program projects and centers. A second level of review will be made by an appropriate national advisory council.

AWARD CRITERIA

Applications will compete for available funds with all other approved applications. The following will be used in making funding decisions:

- o Quality of the proposed project as determined by peer review

- o Availability of funds

- o Program balance among research areas of the announcement

INQUIRIES

Written and telephone inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

Paul L. Nichols, Ph.D

Developmental Neurology Branch

National Institute of Neurological Disorders and Stroke

Federal Building, Room 8C08

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Muscle Biology Program
National Institute of Arthritis and Musculoskeletal and Skin Diseases
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Direct inquiries regarding fiscal matter to:

Patricia P. Driscoll
Grants Management Branch
National Institute of Neurological Disorders and Stroke
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Grants Management Branch
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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.853 ("Clinical Research Related Neurological Disorders") and 93.854 ("Biological Basis Research in the Neurosciences"). Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-150, 42 USC 241 and 285) and administered under PHS grant policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

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