

PROGRAM ANNOUNCEMENT TITLE: ROLE OF MUSCULOSKELETAL
MICROVASCULATURE IN FITNESS AND DISEASE

PA NUMBER: PA-02-104

RELEASE DATE: May 2, 2002

EXPIRATION DATE: July 30, 2005

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

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

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

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

THIS PA CONTAINS THE FOLLOWING INFORMATION

- o Purpose of the PA
- o Research Objectives
- o Mechanisms of Support
- o Eligible Institutions
- o Individuals Eligible to Become Principal Investigators
- o Where to send Inquiries
- o Submitting an Application
- o Peer Review Process
- o Review Criteria
- o Award Criteria
- o Required Federal Citations

PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) encourage investigator-initiated research grant applications on the role of musculoskeletal microvasculature in fitness and disease. An important area is to characterize changes in skeletal muscle perfusion as a result of disease, injury, or exercise training. Responses to this program announcement may include studies in appropriate animal models or preclinical or clinical studies.

RESEARCH OBJECTIVES

Background

Skeletal muscles require strikingly different levels of nutrients and oxygen depending on their level of activity. Research shows that muscle self-adapts in many ways, responding to changes in activity patterns. This includes changes in the protein mass and composition of muscle. There is also significant change in skeletal muscle vasculature, including an increase in capillary density. The change in muscle vasculature allows an increased flow of blood and nutrients into muscles during exertion, supporting an increased level of force and delaying fatigue. Decreased activity, resulting from injury or disease, results in muscle atrophy and a decrease in the density of capillaries. The level of physical activity also has a role in fluid circulation in other musculoskeletal structures, especially poorly vascularized regions such as tendons and joints.

Recent studies found increased amounts of angiogenic factors following increased skeletal muscle activity. Researchers detected increased concentrations of vascular endothelial growth factor, fibroblast growth factor-2, and transforming growth factor-beta-1. While the regulating mechanisms in this response are not clear, present data indicate reduced oxygen tension, increased average calcium concentrations, and other metabolic alterations in the skeletal muscle as possible stimuli. Different exercise-associated stimuli may all contribute to exercise-induced angiogenesis in skeletal muscle, possibly through differing factors and mechanisms. Understanding these processes is important for the elucidation of mechanisms mediating exercise responsiveness in skeletal muscle, but also for the potential that such understanding might bring to the treatment and prevention of human diseases.

Alterations in capillary basal lamina of skeletal muscle are seen in polymyositis, periodic paralysis, and Duchenne muscular dystrophy (DMD). Depending on the disease, there may be endothelial thickening or decrease in the density of capillaries. Recent work suggests that severity of skeletal muscle disease may be related to changes in muscle microcirculation. In one mouse model for DMD, the muscles show decreased levels of nitric oxide synthase, which has a role in regulating blood flow. Earlier research indicated that the highly restricted microvasculature in skeletal muscles of this mouse has a very negative effect on general health, producing cardiomyopathy and premature death in the mouse model. This suggests that DMD and other skeletal muscle diseases might increase resistance to blood flow, resulting in further damage to muscles and generalized symptoms. Alterations in muscle microcirculation may also play a role in the pathology of obesity and the development of diabetic complications such as peripheral neuropathy and the diabetic foot.

Scope and Objectives

This initiative encourages applications that clarify two aspects of musculoskeletal microcirculation. One aim is to understand and characterize how injuries, disease and different levels of physical activity result in changes in the microcirculation within skeletal muscle and other musculoskeletal tissues. A second aim is to determine the role of such changes in maintaining or compromising health. The announcement encourages projects that explore molecular and genomic mechanisms involved in cellular changes in musculoskeletal fluid circulation in response to disease, overuse injuries, or changing patterns of physical activity. This includes mechanisms responsible for the detection and signaling of changes in levels of substances such as oxygen and calcium, and the mechanisms that mediate adaptive changes in metabolism, oxygen sensing, and gene expression.

Responses to this program announcement may include studies in appropriate animal models or preclinical or clinical studies in patients. Investigators with diverse scientific interests are invited to apply their expertise to basic, applied, and clinical research to enhance understanding changes in musculoskeletal microvasculature that occurs due to illness, injury, or altered physical activity.

Examples that illustrate possible areas of research are presented below. They are intended only to provide a broad direction for research and should be considered illustrative and not restrictive.

- o Influence of muscle injury or disease on the plasticity of the skeletal muscle vascular system.

- o Studies on dynamic interrelationships between patterns of skeletal muscle activity and its vasculature and perfusion.

- o Studies to improve understanding of changes in circulation within the musculoskeletal system in response to patterns of use. This includes studies on the mechanisms involved in altered microvasculature and extra-vascular circulation in muscle, bone, and joints. Investigators should explore differences due to endurance and resistance training.

- o Development and validation of appropriate animal models to examine changes in skeletal muscle microvasculature due to disease and patterns of physical activity.

- o Characterization in muscle of the functional and metabolic consequences of exercise and disease-related changes in skeletal muscle microvasculature.

- o Improved quantitative measures of vascular changes in skeletal muscle and blood flow heterogeneity, including dynamic measures.

- o Using improved imaging techniques to better characterize and understand changes in musculoskeletal fluid circulation due to injury, disease or physical activity.

- o Exploring relationships between inflammatory cells, muscle cell death, and blood vessels.

- o Characterize the role of healthy and diseased skeletal muscle in defining total peripheral resistance.

- o Elucidation of the signal transduction, gene regulating, and mitochondrial mechanisms that mediate oxygen sensing in skeletal muscle, and of the time course and oxygen level threshold for adaptive changes in cellular, local, or systemic responses.

- o Identification and characterization of cellular mechanisms that may regulate vascular tone in response to intermittent hypoxia such as the nitric oxide synthase system and the microsomal electron transporting systems associated with P450 enzymes.

- o Influence of altered skeletal muscle blood flow on its metabolism and response to circulating factors.

- o Studies to understand the effects of obesity, weight loss or gain on parameters of skeletal muscle microvasculature, perfusion and interaction with muscle metabolism.

- o Studies to extend knowledge concerning the pathology, mechanism and heterogeneity of microvascular dysfunction in skeletal muscle beds secondary to diabetes, and the metabolic consequences of this dysfunction.

MECHANISMS OF SUPPORT

This PA will use the NIH individual research project grant (R01) and the program project grant (P01) award mechanisms. As an applicant, you will be solely responsible for planning, directing, and executing the proposed project.

This PA uses just-in-time concepts. It also uses the modular 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 format. Otherwise follow the standard instructions for completing the PHS 398 grant application form.

Applications for program project grants may only be submitted from domestic organizations and investigators are requested to contact the NIAMS or NIDDK representative listed under INQUIRIES as early as possible in the planning stages.

ELIGIBLE INSTITUTIONS

You may submit an application 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

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.

WHERE TO SEND INQUIRIES

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

Direct your questions about scientific/research issues to:

Richard W. Lymn, Ph.D.
Muscle Biology Program
One Democracy Plaza

6701 Democracy Blvd. Suite 801
Bethesda, MD 20892
Telephone: (301) 594-5128
FAX: (301) 480-4543
Email: LymnR@mail.nih.gov

Maren R. Laughlin, Ph.D.
Director, Metabolism Program
National Institute of Diabetes and Digestive and Kidney Diseases
6707 Democracy Blvd., Room 6101, MSC 5460
Bethesda, MD 20892-5460
Telephone (301) 594-8802
FAX: (301) 480-3503
Email: Maren.Laughlin@nih.gov

o Direct your questions about peer review issues to:

Tommy Broadwater, Ph.D.
Scientific Review Branch,
National Institute of Arthritis and Musculoskeletal and Skin Diseases
One Democracy Plaza
6701 Democracy Blvd. Suite 801
Bethesda, MD 20892
Telephone: (301) 594-4953
FAX (301) 480-4543
Email: broadwatert@mail.nih.gov

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

Melinda Nelson
Grants Management Officer
National Institute of Arthritis and Musculoskeletal and Skin Diseases
One Democracy Plaza
6701 Democracy Blvd. Suite 801
Bethesda, MD 20892
Telephone: (301) 594-3535
FAX: (301) 480-5450

Email: nelsonm@mail.nih.gov

Denise Payne

Grants Management Specialist

NIDDK, NIH

2 Democracy Blvd, room 733, MSC 5456

Bethesda, MD 20892

Telephone: 301-594-8845

Email: payned@extra.nidDK.nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). 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.

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 GRANT APPLICATIONS: R01 Applications requesting up to \$250,000 per year in direct costs must be submitted in a modular grant format. The modular 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 received by or 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 application already reviewed, but such application must include an Introduction addressing the previous critique.

PEER REVIEW PROCESS

Applications submitted for this PA will be assigned on the basis of established PHS referral guidelines. An appropriate scientific review group 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 the initial merit review, all applications will:

- o Receive a written critique
- 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 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 your application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals:

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

The scientific review group will address and consider each of these criteria in assigning your application's overall score, weighting them as appropriate for each application. Your 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, you 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 your study address an important problem? If the aims of your application are achieved, how do they advance scientific knowledge? 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? Do you acknowledge potential problem areas and consider alternative tactics?

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

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

(5) ENVIRONMENT: Does the scientific environment in which your 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?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, your application will also be reviewed with respect to the following:

PROTECTIONS: 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.

INCLUSION: 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. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria included in the section on Federal Citations, below)

DATA SHARING: The adequacy of the proposed plan to share data.

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

MONITORING PLAN AND DATA SAFETY AND MONITORING BOARD: Research components involving Phase I and II clinical trials must include provisions for assessment of patient eligibility and status, rigorous data management, quality assurance, and auditing procedures. In addition, it is NIH policy that all clinical trials require data and safety monitoring, with the method and degree of monitoring being commensurate with the risks (NIH Policy for Data Safety and Monitoring, NIH Guide for Grants and Contracts, June 12, 1998: <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>).

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 AMENDMENT "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html>); a complete copy of the updated Guidelines are available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.

The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN

SUBJECTS: 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>.

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.

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 No. 93.846 and No. 93.847 and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. 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 described at <http://grants.nih.gov/grants/policy/policy.htm> and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. 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.

[Return to Volume Index](#)

[Return to NIH Guide Main Index](#)