

SKELETAL MUSCLE PERFUSION, AGING AND CARDIOVASCULAR DISEASE

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National Institute on Aging

National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institute of Diabetes and Digestive and Kidney Disease

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

PURPOSE

The National Institute on Aging (NIA), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) invite exploratory research grant applications (R21) for studies of whether aging and/or chronic diseases common to old age, may negatively impact on skeletal muscle perfusion and thereby lead to potential metabolic disorders or limit physical performance in older persons. The current understanding of potential changes in skeletal muscle perfusion in old age and its consequences remains equivocal in nature. With the recent advent of improved tools to measure skeletal muscle perfusion and to examine the muscle microvasculature, it is anticipated that exploratory studies utilizing these new methodologies will help to identify the most promising experimental approaches to address fundamental issues regarding the skeletal muscle microvasculature and blood supply in old age.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This program announcement (PA), Skeletal Muscle Perfusion, Aging and Cardiovascular Disease, is related to the priority areas of physical activity and fitness and diabetes and chronic diseases disabling conditions. Potential applicants may obtain a copy of "Healthy People 2000" at <http://odphp.osophs.dhhs.gov/pubs/hp2000>.

ELIGIBILITY REQUIREMENTS

Applications for exploratory grants (R21) 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. Applications may include collaborative arrangements between scientists from a single institution or multiple institutions. Simultaneous submission of the same research project as both an exploratory grant and a regular research grant (R01) is not permitted.

MECHANISM OF SUPPORT

The mechanism of support will be the NIH exploratory grant mechanism (R21). Applicants may request up to \$150,000 per year in direct costs when applications are from a single institution with no collaborating institutions and \$175,000 when there are two or more institutions collaborating. Specific application instructions have been modified to reflect "MODULAR GRANT" and "JUST-IN-TIME" streamlining efforts being examined by NIH. Complete and detailed instructions and information on Modular Grant applications can be found at:

<http://grants.nih.gov/grants/funding/modular/modular.htm>. Because the nature and the scope of the research proposed in response to this PA may vary, it is anticipated that the size of the awards will vary as well. The total project period for an R21 application submitted in response to this PA may not exceed two years. Responsibility for the planning, direction, and execution of the proposed R21 project will be solely that of the applicant. These grants are non-renewable and continuation of projects developed under this program will be through the traditional unsolicited grants program.

FUNDS AVAILABLE

Approximately \$750,000 in total costs for the first year of funding will be made available by the National Institute on Aging to fund applications submitted in response to this PA. Although NIAMS and NIDDK have not set aside specific funds for this announcement, individual applications that are assigned to either institute will be considered for funding along with other program priorities based upon their relative scientific merit. Awards made will be contingent upon availability of funds and the receipt of a sufficient number of applications of outstanding scientific and technical merit. Direct costs will be awarded in modules of \$25,000, less any overlap or other necessary administrative adjustments.

RESEARCH OBJECTIVES

Background

The performance of a wide variety of tasks require that pulmonary function and cardiac pumping capacity adapt to the oxygen and nutrient demands of the contracting muscle groups. The ability of active skeletal muscle to meet its metabolic and functional demands also depends on the function of its own microvasculature. For example, changes in capillary density or altered responsiveness to local mediators of blood flow could limit the supply of blood and nutrients to skeletal muscle. Therefore, under normal circumstances, the lungs, the heart and the peripheral circulation have to work together to ensure adequate blood supply to contracting muscles. In older persons, an insufficient blood supply to skeletal muscle may contribute to some metabolic disorders (e.g., insulin insensitivity by limiting peripheral glucose uptake) and to physical functional problems. Potential mechanisms underlying compromised muscle blood flow in the elderly could involve: 1) age-related reductions in skeletal muscle mass and/or detrimental changes in its intrinsic properties, 2) age-associated dysfunction of the central and peripheral circulation, and 3) secondary effects of chronic diseases common to old age (e.g., hypertension, diabetes). Unfortunately there is limited data on if or how skeletal muscle perfusion changes with increasing age and/or with diseases common to old age, such as congestive heart failure, peripheral vascular disease, pulmonary disease and diabetes. Thus a clear understanding of the metabolic and physical functional consequences of such changes is lacking, as well.

To address these issues, the NIA organized the workshop, "Changes in Skeletal Muscle Blood Supply with Aging and Disease" which was held on May 12-13, 1998. The specific goals of this workshop were to convene investigators in muscle physiology and cardiovascular research to review the current knowledge base on the regulation of blood flow to muscle and structure/function of the skeletal muscle microvasculature as well as, to identify future research directions in elucidating the role of impaired skeletal muscle perfusion in physical functional problems of the elderly. The specific research areas discussed included: 1) changes in the central and peripheral regulation of skeletal muscle blood flow with advancing age, 2) age-related changes in the structure and function of the skeletal muscle microvasculature, and 3) impact of chronic diseases on skeletal muscle blood supply and its regulation. This PA seeks to promote the research priorities identified at the workshop.

Objectives and Scope

This initiative will provide research support for exploratory/pilot studies of potential changes in skeletal muscle blood flow/perfusion due to aging and/or chronic diseases common to old age. Applications submitted in response to this PA should explore the mechanism(s) by which changes in skeletal muscle blood supply could contribute to metabolic and/or physical functional problems often noted in older persons. Topics of interest include, but are not limited to:

- o Characterization of the metabolic and/or physical functional consequences of age-associated and disease-related changes in the skeletal muscle microvasculature
- o Studies of the interrelationship(s) between pulmonary, cardiac and skeletal muscle function during rest and at times of submaximal exercise in older individuals
- o Development of novel rehabilitation strategies to improve hemodynamics in older patients with vascular diseases (e.g., peripheral vascular disease, claudication)
- o Exploration of factors/mechanisms associated with age-related decreases in maximum cardiac output that may limit skeletal muscle perfusion and function. These mechanisms may include age-related alterations in left ventricular end diastolic volume, competency of venous valves and arterial stiffness
- o Investigation of changes in autonomic responsiveness (e.g., maximum heart rate, left ventricular contractility, ejection fraction) that may influence blood supply to skeletal muscle.
- o Potential changes in pulmonary function related to aging or disease, that may affect adequate oxygen delivery to active skeletal muscle.
- o Influence of age, physical activity/inactivity and or chronic diseases on the plasticity of the skeletal muscle vascular system.
- o Influence of altered blood flow on progression of diabetic complications such as neuropathy and diabetic foot.
- o Development and validation of appropriate animal models to examine changes in skeletal muscle microvasculature due to aging and/or disease.
- o Improved quantitative measures of vascular changes in skeletal muscle and blood flow heterogeneity, including dynamic measures.

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 is provided 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 "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and in the NIH Guide for Grants and Contracts, Volume 23, Number 11, March 18, 1994, <http://grants.nih.gov/grants/guide/notice-files/not94-100.html>.

Investigators also may obtain copies of the policy from the program staff listed under INQUIRIES. Program staff may provide additional information concerning the policy.

APPLICATION PROCEDURES

Applications are to be submitted on 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, Phone (301) 435-0714, Email: GRANTSINFO@NIH.GOV. Applications are also available on the internet at <http://grants.nih.gov/grants/funding/phs398/phs398.html>.

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)

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

SPECIFIC APPLICATION INSTRUCTIONS FOR MODULAR GRANTS

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.

BUDGET INSTRUCTIONS

As specified in the MECHANISM OF SUPPORT, applicants may request up to \$150,000 or \$175,000 in direct costs based on the number of collaborating institutions. These costs should be requested in \$25,000 modules, up to a total direct cost request of \$150,000 per year when there is a single institution involved (no collaborating institutions), or up to a total direct cost request of \$175,000 when two or more institutions are collaborating. 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 \$150,000 or \$175,000 based on the number of collaborating institutions) 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.

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 key 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 key 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.

REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established Public Health Service referral guidelines. Applications that are complete will be evaluated for scientific and technical merit by an appropriate peer review group convened in accordance with 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:

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

Chhanda Dutta, PhD
Geriatrics Program
National Institute on Aging
7201 Wisconsin Avenue, Suite 3E-327 MSC 9205
Bethesda, MD 20892-9205
Telephone: (301) 435-3048
Email: cd23z@nih.gov

Richard W. Lymn, Ph.D.
Muscle Biology Program
National Institute of Arthritis and Musculoskeletal and Skin
Diseases 45 Center Drive, MSC 6500
Bethesda, MD 20892-6500
Telephone: (301) 594-5128
FAX: (301) 480-4543
Email: LymnR@exchange.nih.gov

Maren R. Laughlin, Ph.D.
Metabolism Program
National Institute of Diabetes, and Digestive and Kidney Disease
Room 6101, MSC 5460
6707 Democracy Boulevard
Bethesda, MD 20892-5460
Telephone: (301) 594-8802
Email: maren.laughlin@nih.gov

Direct inquiries regarding fiscal matters to:

Cynthia Riddick
Grants and Contracts Management Office
National Institute on Aging
7201 Wisconsin Avenue, Suite 2N212, MSC 9205
Bethesda, MD 20892-9205
Telephone: (301) 496-1472
FAX: (301) 402-3672
Email: Riddickc@exmur.nia.nih.gov

Ms. Melinda Nelson
Grants Management Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, MSC 6500
Bethesda, MD 20892-6500
Telephone: (301) 435-5278
FAX: (301) 480-5450
Email: NelsonM@exchange.nih.gov

Mary Kay Rosenberg
Grants Management Specialist
NIDDK
Building 45, Room 6AS-49D
45 Center Drive, MSC 6600
Bethesda, MD 20892-6600
(301) 594-8891 phone
(301) 480-3504 FAX
Email: RosenbergM@extra.niddk.nih.gov

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.866, Aging Research, No. 93.846, Arthritis and Musculoskeletal and Skin Diseases Research and No. 93.847, Diabetes, and Digestive and Kidney Disease Research. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410), as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants 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.

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, 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](#)