

Microgravity: Supplements to NIAMS SCORs and P01s

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National Institute of Arthritis and Musculoskeletal and Skin Diseases

PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), in collaboration with the Life Sciences Division of the National Aeronautics and Space Administration (NASA), invites investigators already supported under an NIAMS Specialized Center of Research (SCOR), an NIAMS Program Project, or individuals who make appropriate collaborative arrangements with SCOR or Program Project personnel to supplement these grants with no more than one project focusing on the effects of microgravity on the musculoskeletal system. Supplements may include basic, applied, and clinical research projects.

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 Request for Applications (RFA), Research on the Effects of Microgravity on the Musculoskeletal System, is related to the priority area of chronic disabling conditions. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0) or "Healthy People 2000" (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

Only investigators currently receiving support via an NIAMS SCOR or NIAMS Program Project may apply for supplemental funding. The parent project must have a minimum of three years of support remaining at the time of award. Collaborative arrangements may be utilized when appropriately justified. The specific aims of the supplemental award must focus on the areas addressed under RESEARCH OBJECTIVES described below. The proposed research must be clearly integrated with the existing goals of the funded SCOR or Program Project and not a totally independent project which might be better supported as a Regular Research Grant (R01).

MECHANISMS OF SUPPORT

Support will be offered through a supplemental award given to an already funded SCOR (P50) or Program Project (P01). Because this is a special supplement, please contact the program official responsible for the parent grant before applying. The maximum size of a supplemental award will be \$50,000 direct costs. Only one supplement application may be submitted for each parent grant. The duration of the supplement should not extend beyond the total project period of the parent grant. The anticipated award date is July 1, 1994.

In addition to the requirements stated in this RFA, awards will be administered under PHS grants policy as stated in the Public Health Service Grants Policy Statement, DHHS Publication No. (OASH) 90-50-000, revised October 1, 1991. This RFA is a one-time solicitation. Future unsolicited competing continuation applications will compete with all investigator-initiated applications and be reviewed according to the customary peer review procedures.

FUNDS AVAILABLE

Up to \$300,000 for the first-year and additional approved expenses for subsequent years has been committed to fund applications submitted in response to this RFA. The NIAMS, in collaboration with NASA, plans to make up to four supplemental awards in FY 1994, with a first year maximum direct cost of \$50,000 each. Funding of grants is contingent upon receipt of highly meritorious applications. Funding beyond the first and subsequent years of the grant will be contingent upon satisfactory progress during the preceding years and the availability of funds.

RESEARCH OBJECTIVES

Space travel encompasses many exciting technological challenges and opportunities. As the U.S. Space Program prepares for extended duration space flights on the Space Shuttle, Space Station Freedom, and on exploration missions to the Moon and Mars, it is important that life sciences research provide a thorough understanding of the many physiologic changes that occur in a microgravity environment. This research should also lead to development of effective countermeasures to any effects that may be detrimental to the functional capacity, health, or well-being of crew members. The musculoskeletal system has the capacity to adapt its structural and functional properties in accordance with the type and degree of stimuli imposed on it. Prolonged space travel is essentially a period of significant unloading of the musculoskeletal system. Exposure to weightlessness results in structural and functional adaptations that place the musculoskeletal system on the low end of the continuum ranging from complete disuse to maximal capacity. Evidence from previous space flights and ground-based research indicates that the musculoskeletal system is functionally impaired with increasing duration of weightlessness.

Space flight has been consistently accompanied by bone atrophy and negative calcium balance. Bone density may decrease by as much as 10 percent per year. This change in bone density is preceded by significant and more rapid skeletal muscle weakening and atrophy. Prolonged exposure to weightlessness diminishes functional capacity, performance and endurance of the musculoskeletal system, even at submaximal loads, and thus elicits concern about the health and well-being of space travellers especially as space flight is extended in time.

A workshop on the "Effects of Space Travel on the Musculoskeletal System" was co-sponsored by the NIAMS and NASA in October, 1990. The workshop provided state-of-the-art knowledge, identified research gaps and windows of opportunity, and recommended future directions for research on understanding the musculoskeletal system's adaptation to exposure to weightlessness, including development of adequate physiologic and performance-based countermeasures. Although there is a good research base of knowledge on the complex bone remodelling process and potential biological agents and factors that may be able to restore or prevent bone loss on earth, more research is required in space applications of these technologies. Considerably less information is available on understanding how force development by skeletal muscle is essential in maintaining bone integrity. Likewise, there is a strong science base regarding muscle physiology but space applications are limited. A workshop summary, *The Effects of Space Travel on the Musculoskeletal System*, has been published (NIH Publication No. 93-3482, November 1992) and is available upon request to the Program Officials identified below under INQUIRIES.

The NIAMS, in collaboration with NASA, is interested in soliciting supplemental grant applications, from established SCORs and Program Projects, with a research focus is on understanding the musculoskeletal system's adaptation to microgravity environments.

The objective of this RFA is to stimulate basic, applied, and clinical research on elucidating the effects of microgravity on the musculoskeletal system. Development of mechanism-related hypotheses encompassing both basic and applied science is desirable. While the research focus is on reduced gravity conditions, well justified studies on musculoskeletal responses to

hypergravity conditions may be instrumental in understanding the pathogenesis of bone and skeletal muscle weakness and loss during exposure to microgravity environments. A key feature of the basic research component is understanding the cellular mechanisms whereby alterations in the musculoskeletal system are evoked in response to external loading and loading histories. For example, how does loading or lack of it affect cellular processes and regulatory factors that control turnover of matrix and contractile proteins? Basic research would focus on the physiologic changes of bone and skeletal muscle in cell and tissue cultures that occur in a low or high gravity environment.

Applicants are also encouraged to engage in appropriate applied/clinical studies addressing microgravity-induced osteopenia and skeletal muscle atrophy in whole animal and human experiments. Utilization of available technologies including, but not limited to, the following are encouraged: simulations of weightlessness (e.g., suspension limb model), centrifugation (alterations in 'g' forces), and bed rest. Applicants may collaborate with NASA scientists (based on availability of resources), especially in gaining access to hospital beds in a clinical setting and low or high gravity environment facilities.

As with other projects in the SCOR or Program Project, there should be a demonstrated interaction with other projects and/or core facilities that make the supplement integral to the activities of the team of funded investigators. Each funded grant may be supplemented with no more than one project focusing on the effects of microgravity on the musculoskeletal system.

Examples of research activities identified by the Workshop include, but are not limited to:

- Development of therapeutic agents that restore bone loss and muscle weakness;

- Quantification of rate, magnitude, and cellular origins of bone and skeletal muscle cell loss;

- Influence of skeletal muscle second messengers on bone growth;

- Hormonal and growth factor effects on calcium homeostasis, and bone and muscle cell function and metabolism, including glucocorticoid-induced osteopenia and muscle atrophy;

- Characterization of bone loading in bedrest subjects;

- Bone and muscle cell responses to stress and gravity;

- Evaluation of 3-D structure and integrity of the musculoskeletal system and constituent tissues;

- Bone and muscle cell expression, including characterization of cellular receptors, signal transduction and messengers for gravity; and

- Alterations in blood flow and its impact on cellular metabolism.

These areas of research are neither prioritized nor meant to be restrictive. Investigators are encouraged to submit applications in any meritorious area of research responsive to the general research objectives of this RFA.

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 are 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 Form PHS 398 (rev. 9/91) 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, and 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

The research grant application form PHS 398 (rev. 9/91) is to be used in applying for these grants. Application kits are available at most institutional offices of sponsored research and may be obtained from the Office of Grants Inquiries, Division of Research Grants, National Institutes of Health, Westwood Building, Room 449, Bethesda, MD 20892, telephone 301/496-7441.

The RFA label available in the application kit must be affixed to the bottom of the face page. Failure to use the label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, RFA AR-93-007, Research Supplements to NIAMS Specialized Centers and Program Projects, must be typed on line 2a of the face page of the application form and the YES box should be checked.

The completed and signed, typewritten original application and five signed, exact, clear, single-sided photocopies must be sent or delivered in one package to:

DIVISION OF RESEARCH GRANTS
National Institutes of Health
Westwood Building, Room 240
Bethesda, MD 20892**

** Applicants who wish to use express mail or courier service should change the zip code to 20816.

At time of submission, two additional exact copies of the application must also be sent under separate cover to:

Dr. Tommy Broadwater
Chief, Review Branch Extramural Program
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 404
5333 Westbard Avenue
Bethesda, MD 20892**

Applications must be received by Sept 14, 1993. If an application is received after that date, it will be returned to the applicant without review. The Division of Research Grants (DRG) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, it is allowable to submit the same project as both an R01 and as a component project of a program project (P01). The DRG will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications previously reviewed. Such applications must not only include an introduction addressing the previous critique but also be responsive to this RFA.

REVIEW PROCEDURES

Upon receipt, applications will be reviewed by the DRG for completeness. Incomplete applications will be returned to the applicants without further consideration. Evaluation for responsiveness to the program requirements and criteria stated in the RFA is an NIAMS staff function. If the application is not responsive to the RFA, NIAMS staff will contact the applicant to determine whether it should be returned to the applicant or held until the next regular receipt date and reviewed in competition with all other unsolicited applications.

Those applications that are complete and responsive will be evaluated in accordance with the criteria stated below for scientific and technical merit by an appropriate peer review group convened by the NIAMS. Applications may be subject to triage by an NIAMS peer review group to determine scientific merit relative to other applications received in response to this RFA. If the number of applications submitted is large compared to the number of awards to be made, a preliminary scientific peer review may be conducted and applications withdrawn from further competition if not competitive for the award. The NIAMS will notify the applicant and institutional official of this action.

Those applications judged to be competitive will be reviewed for scientific and technical merit in

accordance with the usual NIH peer review procedures by an initial review group specifically convened for this RFA. Following initial review, applications will receive a second level review by the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council unless not recommended for further consideration by the initial review group.

Review criteria for RFAs are generally similar as those for unsolicited investigator-initiated research grant applications and include:

Integration of the supplemental project with the other components of the parent grant;

Scientific, technical, or medical significance and originality of the proposed research;

Appropriateness and adequacy of the experimental approach and methodology proposed to conduct the research;

Qualifications and research experience of the Principal Investigator and staff, particularly, but not exclusively, in the area of the proposed research;

Availability of resources necessary to perform the proposed research;

Appropriateness of the proposed budget and duration in relation to the proposed research; and

If an application involves activities that could have an adverse effect upon humans, animals, or the environment, the adequacy of the proposed means for protecting against or minimizing such effects.

In addition, for foreign applications, the following criterion applies:

Uniqueness of research such that it can only be performed outside of the United States.

Schedule

Application Receipt Date:	September 14, 1993
Initial Review:	Feb/Mar, 1994
Second Level Review:	May/Jun, 1994
Anticipated Award:	July 1, 1994

AWARD CRITERIA

Applications will compete for available funds with all other applications responsive to this RFA. The following criteria will be considered in the making of funding decisions:

Quality of the proposed project as determined by peer review;
Availability of funds; and
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 for the NIAMS regarding programmatic issues to:

Stephen L. Gordon, Ph.D.

Chief, Musculoskeletal Diseases Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 407
5333 Westbard Avenue
Bethesda, MD 20892
Telephone: (301) 402-3338

Richard W. Lymn, Ph.D.
Chief, Muscle Biology Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 403
5333 Westbard Avenue
Bethesda, MD 20892
Telephone: (301) 402-3346

Julia B. Freeman, Ph.D.
Centers Program Director
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 403
5333 Westbard Avenue
Bethesda, MD 20892
Telephone: (301) 402-3348

Direct inquiries for the NASA regarding programmatic issues to:

Victor S. Schneider, M.D.
Space Physiology Program Scientist
Life Sciences Division
National Aeronautics and Space Administration
Code SBM
300 E Street, S.W. Washington, D.C. 20546
Telephone: (202) 358-2359

Direct inquiries for the NIAMS regarding fiscal matters to:

Ms. Diane M. Watson
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 732A
5333 Westbard Avenue
Bethesda, MD 20892
Telephone: (301) 402-3352

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846, Arthritis, Musculoskeletal and Skin Diseases Research. Awards will be made under the authority of the Public Health Service Act, Title III, Section 301 (Public Law 410, 78th Congress, as amended, 42 USC 241) and administered under PHS grants policies and Federal regulations 42 CFR Part 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.