

NEW RESEARCH STRATEGIES FOR EVALUATION AND ASSESSMENT OF BONE QUALITY

Release Date: December 31, 2001

RFA: RFA-AR-02-002

National Institute of Arthritis and Musculoskeletal and Skin Diseases

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

National Institute of Dental and Craniofacial Research

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

Letter of Intent Receipt Date: February 21, 2002

Application Receipt Date: March 21, 2002

THIS RFA USES "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. MODULAR INSTRUCTIONS MUST BE USED FOR RESEARCH GRANT APPLICATIONS UP TO \$250,000 PER YEAR. MODULAR BUDGET INSTRUCTIONS ARE PROVIDED IN SECTION C OF THE PHS 398 (REVISION 5/2001) AVAILABLE AT <http://grants.nih.gov/grants/funding/phs398/phs398.html>.

PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) invites research applications that provide novel means to assess bone quality and elucidate the relationships among disease- and aging-related changes in bone quality, gender-related variations in bone quality, and increased bone fragility and fracture susceptibility. Current tools for the precise assessment of fracture risk are limited. In order to target high risk populations for preventive or therapeutic interventions, it is necessary to have tools that are able to assess bone strength and quality. Applications may be in the form of individual research projects (R01) or exploratory/developmental research grants (R21).

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 RFA, "New Research Strategies for Evaluation and Assessment of Bone Quality," is

related to the priority area of chronic diseases. 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. Applicants also may collaborate, through consultation or contractual agreements, with investigators at foreign institutions. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators. Participation in the program by investigators at minority institutions is strongly encouraged.

MECHANISMS OF SUPPORT

The mechanisms of support will include the investigator-initiated research project grant (R01) and the exploratory/developmental research grant (R21).

R01 Applications. The individual research grant (R01) is a specific, circumscribed project to be performed by the named investigator(s) who has a specific interest and competency in an area of interest to this RFA. The total project period for an R01 application submitted in response to this RFA may not exceed 5 years. Future unsolicited competing continuation applications will compete with all investigator-initiated applications and be reviewed according to the customary peer review procedures. Because the nature and scope of the research proposed in response to this RFA may vary, it is anticipated that the size of an R01 award will vary also. Modular budgeting procedures apply to grants up to \$250,000. Specific R01 application instructions have been modified to reflect "modular grant" and "just-in-time" streamlining efforts. Complete instructions and information on modular grants can be found at <http://grants.nih.gov/grants/funding/modular/modular.htm>. Direct costs will be awarded in modules of \$25,000, less any overlap or other necessary administrative adjustments. F and A costs will be awarded based on the negotiated rates.

R21 Applications. The purpose of the R21 projects solicited under this RFA is to gather preliminary data leading to the development of an investigator-initiated research project (R01). Use of this mechanism is recommended by investigators experienced in bone structure/imaging /osteoporosis research who wish to adapt or apply novel methodologies to study bone quality. It is also recommended for investigators with relevant expertise (e.g., imaging of other tissues,

engineers, or others) interested in developing a program for assessment of bone quality. Exploratory/developmental research grants (R21) may not exceed \$100,000 per year (4 modules) in direct costs, not including facilities and administrative (F&A) costs for collaborating institutions, if any. The total project period for an R21 application submitted in response to this RFA may not exceed 3 years. These grants are nonrenewable and continuation of projects developed under the R21 program should be through the traditional unsolicited (R01) grant programs. Exploratory/developmental studies are not intended for large-scale undertakings or to support or supplement ongoing research. Instead, investigators are encouraged to explore the feasibility of an innovative research question or approach that may not be at a stage advanced enough to compete as a standard research project grant (e.g., R01).

FUNDS AVAILABLE

It is anticipated that for FY 2002, approximately \$1.2 million (total costs) will be available for the first year of support for this initiative. The specific number of grants to be awarded will depend upon the merit and scope of the applications received and on the availability of funds for this purpose. An applicant using the R01 mechanism may request a project period of up to 5 years and a budget for direct costs of up to \$250,000 per year. Exploratory/developmental research grants using the R21 mechanism may not exceed \$100,000 per year in direct costs, not including F and A costs for collaborating institutions, if any. Total project period for an R21 application submitted in response to this RFA may not exceed 3 years. Awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications of interest to NIAMS. At this time, it is not known if this RFA will be reissued.

RESEARCH OBJECTIVES

The progressive or sudden loss of bone very commonly leads to osteoporosis, a condition characterized by increased skeletal fragility and susceptibility to fracture. Osteoporosis and its consequences are a significant cause of frailty, morbidity, and even mortality among the elderly. However, while reduced bone mass is important both in contributing to and predicting an enhanced risk of fracture, low bone mass alone is not a sufficient explanation for osteoporotic fractures. This is exemplified by the substantial overlap in bone density between normal individuals and those who sustain hip and other osteoporotic fractures. Recently, gender-related differences in fracture susceptibility have been identified that cannot be explained by simple differences in bone size. It has become apparent that the conceptual basis of skeletal integrity must be broadened to include, in addition to bone mineral content, qualitative factors that may

impact on bone strength such as geometry, macro and micro-structural organization, distribution of material within bone, biochemical composition, and the burden of unrepaired microdamage.

This RFA is directed towards: (1) stimulating research aimed at elucidating mechanisms of bone fragility and its measurement and (2) developing strategies and methodologies aimed at better identifying those at risk of osteoporosis-related fractures and in need of therapeutic intervention to prevent such fractures. Specifically, this RFA seeks applications for basic and clinical research to identify and evaluate the relationship between measures of bone density and bone quality and/or strategies to modify the bone quality to reduce skeletal fragility and decreased fracture susceptibility. Topics of interest include, but are not limited to:

- o Changes in architecture, mechanical properties, and strength of bone with disease and aging and non-invasive means to determine these properties
- o Evaluation of changes in bone matrix and mineralization and their impact on strength and resistance to microdamage
- o Assessment of the consequences of the accumulation of cortical and trabecular microdamage and their relationship to bone strength and fracture biomechanics
- o Development and application of new technologies for bone quality assessment to be used in monitoring craniofacial development and alveolar bone loss.
- o Development and application of techniques such as histomorphometry, ultrasound, MRI, and QCT to evaluate changes in architecture, bone strength and fracture susceptibility
http://odp.od.nih.gov/consensus/cons/111/111_intro.htm.

Specific Objectives

This initiative will support studies in areas that have the potential to elucidate the nature and consequences of disease- and age-related changes in bone quality and the relationship of such changes to increased bone fragility and fracture susceptibility. The specific objectives of this solicitation are to address the following questions:

- o What changes in bone mineral density, bone matrix, and bone architecture significantly affect the biomechanical properties of bone?

o Are there non-invasive, reproducible imaging markers/methodologies that can be used to assess longitudinal, age-related, and gender-related changes in bone quality with regard to fracture risk?

o Do these non-invasive, reproducible imaging markers/methodologies for bone quality assessment provide a means to explain the discrepancy between bone mineral density and fracture reduction with anti-resorptive therapy?

o How do measurement site and regional heterogeneity influence these non-invasive, reproducible imaging markers/methodologies for assessment of bone quality?

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 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

It is the policy of the 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 or 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 policies.

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. This policy announcement is found in the NIH Guide for Grants and Contracts Announcement dated June 5, 2000, at the following website: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html>.

URLS IN NIH GRANT APPLICATIONS OR APPENDICES

All applications and proposals for NIH funding must be self-contained within specific 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.

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 RFA 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.

LETTER OF INTENT

Prospective applicants are asked to submit, by February 21, 2002, a letter of intent that includes a descriptive title of the proposed research; the name, address, and telephone number of the Principal Investigator; the identities of other key personnel and participating institutions; and the number and title of this RFA. Although a letter of intent is not required, is not binding, does not commit the sender to submit an application, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and avoid conflict of interest in the review. The letter of intent is to be sent (e-mail, fax or post) to Dr. Tommy Broadwater at the address listed under INQUIRIES.

APPLICATION PROCEDURES

Specific application instructions have been modified to reflect "MODULAR GRANT" and "JUST-IN-TIME" streamlining efforts that have been adopted by the NIH. Complete and detailed instructions and information on Modular Grant applications have been incorporated into the PHS 398 (rev. 5/2001). Additional information on Modular Grants can be found at <http://grants.nih.gov/grants/funding/modular/modular.htm>.

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>.

Modular grant applications will request direct costs in \$25,000 modules, up to a total direct cost request of \$250,000 per year for R01 mechanisms and up to a total direct cost of \$100,000 per year for R21 mechanisms. A typical modular grant application will request the same number of modules in each year. 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:

In preparing the R21 application, the Background and Significance Section of application should specifically state how the project represents a new direction for the work performed at the PI's laboratory. This should include a brief section (one page or less) entitled "Qualifications for High Risk" in which the PI specifically addresses the following concerns:

- o Innovation & Novelty: Does the proposed project represent a high degree of innovation and novelty?
- o Departure from current work: Does the proposed project specifically overlap with work from the PI during the last five years? How does the proposed work represent a significant departure from the PI's current line of work?
- o High risk: Explain how the high gain potential of the project, if successful, offsets the high risk of failure.

A Preliminary Data section is not required for the R21 applications but if included, it should not exceed one page.

The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: <http://grants.nih.gov/grants/funding/phs398/label-bk.pdf>.

Submit a signed typewritten original of the application and three 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)

At the time of submission, two additional copies of the application and all five sets of any appendix materials must be sent to:

Dr. Tommy L. Broadwater
Scientific Review Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Room 5AS-25U - MSC 6500
Bethesda, MD 20892-6500

Applications must be received by March 21, 2002. If an application is received after that date, it will be returned to the applicant without review.

The Center for Scientific Review (CSR) will not accept any application in response to the RFA that is essentially the same as on 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 substantial revisions of applications already reviewed, but such applications must include an Introduction addressing the previous critique.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by CSR and responsiveness by NIAMS. If the application is not responsive to the RFA, CSR staff may contact the applicant to determine whether to return the application to the applicant or submit it for review in competition with unsolicited applications at the next review cycle.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the NIAMS in accordance with the review criteria stated below. As part of the initial merit review, all applications will receive a written critique and under a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed, assigned a priority score, and receive a second level review by the NIAMS Advisory Council.

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, weighing 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. R21 applications will be judged by the criteria listed in the "High Risk Arthritis and Musculoskeletal and Skin Diseases Research" solicitation, AR-01-008, found at <http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-01-008.html>.

(1) Significance. Does the proposed 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 methods? Are the aims original and innovative? Does the project challenge existing paradigms or seek to 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?

(6) Protection of Human Subjects. Are there adequate provisions for the protection of human subjects? Is there sufficient attention given to the extent they may be adversely affected by the

project proposed in the application? Applications that fail to comply with this requirement will be designated as incomplete and will constitute grounds for the return of the application without peer review.

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 and in conformance with the NIH policy. Plans for recruitment and retention of subjects will also be evaluated.

- o The adequacy of the provisions for the protection of animal subjects, the safety of the research environment, to the extent they may be adversely affected by the project proposed in the application.

- o The appropriateness of staffing based on the requested percent effort and the personnel budget. The direct costs budget request will be reviewed for consistency with the proposed methods and specific aims. Any budgetary adjustments recommended by the reviewers will be in \$25,000 modules. The duration of support will be reviewed to determine if it is appropriate to ensure successful completion of the requested scope of the project.

SCHEDULE

Letter of Intent Date: February 21, 2002
Application Receipt Date: March 21, 2002
Council Review: September 25, 2002
Earliest Anticipated Start Date: September 30, 2002

AWARD CRITERIA

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 Programmatic priorities

INQUIRIES

Inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to one of the following:

Gayle E. Lester, Ph.D.
Musculoskeletal Diseases Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Room 5AS-43C
Bethesda, MD 20892-6500
Telephone: (301) 594-5055
FAX: (301) 480-4543
Email: gl83g@nih.gov

Guo Zhang, Ph.D.
Program Director
Division of Extramural Research
National Institute of Dental and Craniofacial Research
Natcher Building, Room 4AN-18C
Bethesda, MD 20892-6402
Telephone: (301) 594-0618
FAX: (301) 480-8318
Email: gjo.zhang@nih.gov

Direct inquiries regarding review issues to:

Tommy L. Broadwater, Ph.D.
Scientific Review Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Room 5AS-25U - MSC 6500
Bethesda, MD 20892-6500
Telephone: (301) 594-4953
FAX: (301) 480-4543
Email: broadwat@mail.nih.gov

Direct inquiries regarding fiscal matters to one of the following:

Melinda Nelson

Grants Management Branch

National Institute of Arthritis and Musculoskeletal and Skin Diseases

45 Center Drive, Room 5AS-49F, MSC 6500

Bethesda, MD 20892-6500

Telephone: (301) 594-3535

FAX: (301) 480-5450

Email: nelsonm@mail.nih.gov

Mr. Martin Rubinstein

Office of Grants Management

National Institute of Dental and Craniofacial Research

Natcher Building, Room 4AN-44A

Bethesda, MD 20892-6402

Telephone: (301) 594-4800

FAX: (301) 480-8301

Email: Martin.Rubinstein@nih.gov

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846. 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.

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