

## MECHANISMS OF MINERALIZATION IN BONE

RELEASE DATE: September 4, 2003

RFA Number: RFA-AR-04-001

Department of Health and Human Services (DHHS)

### PARTICIPATING ORGANIZATIONS:

National Institutes of Health (NIH)

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

### COMPONENTS OF PARTICIPATING ORGANIZATIONS:

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

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

CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER(S) 93.846

LETTER OF INTENT RECEIPT DATE: October 21, 2003

APPLICATION RECEIPT DATE: November 18, 2003

### THIS RFA CONTAINS THE FOLLOWING INFORMATION

- o Purpose of this RFA
- o Research Objectives
- o Mechanism of Support
- o Funds Available
- o Eligible Institutions
- o Individuals Eligible to Become Principal Investigators
- o Where to Send Inquiries
- o Letter of Intent
- o Submitting an Application
- o Peer Review Process
- o Review Criteria
- o Receipt and Review Schedule
- o Award Criteria
- o Required Federal Citations

### PURPOSE OF THIS RFA

This RFA is intended to stimulate and support investigation of the mechanisms that mediate and regulate the incorporation of mineral into bone. Recent observations have

underscored the critical contribution of bone mineral to the mechanical properties of bone, including its resistance to fracture. Thus, an improved understanding of the mineralization process could lead to new therapeutic and preventive interventions for reducing the risk of fracture in groups at risk because of bone loss.

## RESEARCH OBJECTIVES

### Background and Rationale

Bone is composed of a protein matrix, which contains embedded crystals of hydroxyapatite, a form of calcium phosphate. The incorporation of the mineral into the matrix is essential for the hardness and rigidity that enable the skeleton to resist gravitational and mechanical loading. Although chemical and physical analyses have revealed many details of the structure and organization of mineral in bone, much remains unclear about the process by which calcium and phosphate ions are sequestered from the soluble phase to form crystals in association with the bone matrix.

In bone formation, osteoblasts first secrete the proteins of the bone matrix, or osteoid, which acquires mineral after forming as a histologically distinct layer. Several proteins have been identified with the property of inhibiting matrix mineralization, suggesting that the potential for precipitation of mineral is inherent in the physiological milieu, and that a counterbalancing inhibition is required to prevent inappropriate formation of insoluble crystals. Indeed, several common pathologies, such as vascular calcification and crystal deposition arthropathies, provide evidence of the importance of appropriate control of mineralization in tissues. Yet it remains unclear whether mineralization of bone principally reflects passive chemical processes, requiring only the presence of appropriate local concentrations of the precipitating ions, or instead, involves active biological processes, requiring higher-order functions of cells and their macromolecular components.

Recent observations indicate that variation in the degree and nature of bone matrix mineralization may be an important determinant of resistance to fracture. Importantly, there are suggestions that some pharmacological agents, widely used to reduce fracture risk, may have their effects in part by altering the quantity or quality of bone mineral. Other work has begun to identify the gene products and molecular pathways that control the formation and maintenance of bone mineral. An improved understanding of these pathways could furnish new principles for the development of preventive and therapeutic measures to improve bone quality and prevent fractures.

### Objectives and Scope

The overall objective of this RFA is to illuminate chemical, macromolecular, and cellular mechanisms that mediate or influence the incorporation of mineral into bone. Specifically, the focus of the initiative is on the osteoblast and its secreted matrix, including intrinsic functions of the osteoblast, its interactions with other cells, and its immediate environment in bone. Excluded from this focus are the consequences of

dietary mineral deficiency and mechanisms of systemic mineral regulation. Although adequate dietary intake and normal systemic levels of calcium and phosphate are important for bone mineralization, a large literature already exists on the physiology and endocrinology of these factors.

In contrast, the focus of this initiative is the mineralization process itself, as it occurs when osteoblasts produce bone, for example, during the remodeling of the mature skeleton, or in the formation of certain flat bones. The distinct mineralization process that occurs in the cartilage of the growth plate regions of long bones is outside the scope of this RFA. Similarly, the mineralization of teeth and the various pathological conditions that arise from inappropriate mineralization of soft tissues are not to be addressed in this initiative. It is recognized that some of the same molecules and similar mechanisms may be important in both bone and other tissues. However, the measure of responsiveness to this RFA will be the potential of proposed studies to illuminate the processes by which bone acquires its mineral component, and with it, its critical physical and mechanical attributes. Of particular interest are approaches that may lead to new diagnostic tools for predicting fracture risk, or to therapeutic or preventive interventions that can reduce fracture risk.

Appropriate research areas may include, but are not limited to, the following (subject to the exclusions noted above):

- o Characterization and analysis of animal models, whether naturally occurring, mutant, or genetically modified, in which variations and/or aberrations of bone mineral properties are observed.
- o Detection and analysis of genetic or environmental factors that influence the mineralization of bone in animals or humans.
- o Investigations of the role in mineralization of specific gene products, such as ion transporters and enzymes, which have the potential to alter local concentrations of extracellular mineral ions.
- o Studies of molecular and cellular mechanisms of mineralization in cell culture models in which the mineralization process can be demonstrated to have strong parallels with that occurring in bone.
- o Studies of the interactions between mineral and components of the bone matrix (collagenous and non-collagenous), and of the possible roles of matrix components in either promoting or inhibiting the mineralization of bone.
- o Analysis of the biological basis for differences in quantity or quality of incorporated mineral that result in differences in the physical and mechanical properties of bone.

## MECHANISM OF SUPPORT

This RFA will use the NIH traditional research project (R01) grant award mechanism. As an applicant you will be solely responsible for planning, directing, and executing the proposed project. This RFA is a one-time solicitation. Future unsolicited, competing-continuation applications based on this project will compete with all investigator-initiated applications and will be reviewed according to the customary peer review procedures. The anticipated award date is July 2004. Applications that are not funded in the competition described in this RFA may be resubmitted as NEW investigator-initiated applications using the standard receipt dates for NEW applications described in the instructions to the PHS 398 application.

This RFA uses just-in-time concepts. It also uses the modular budgeting format. (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 budget format. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at [http://grants.nih.gov/grants/policy/nihgps\\_2001/part\\_i\\_1.htm](http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm).

## FUNDS AVAILABLE

The NIAMS intends to commit approximately \$1 million in FY 2004 to fund three to four new and/or competitive continuation grants in response to this RFA. An applicant may request a project period of up to four years and a budget for direct costs of up to \$250,000 per year. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. Although the financial plans of the NIAMS provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications.

## 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 institutions/organizations
- o Faith-based or community-based organizations

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

o Direct your questions about scientific/research issues to:

William J. Sharrock, Ph.D.  
Musculoskeletal Diseases Branch  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
NIH, DHHS  
One Democracy Plaza  
6701 Democracy Blvd., Suite 800  
Bethesda, MD 20892-4872  
Telephone: (301) 594-5055  
FAX: (301) 480-4543  
Email: [ws19h@nih.gov](mailto:ws19h@nih.gov)

o Direct your questions about peer review issues to:

Teresa Nesbitt, D.V.M., Ph.D.  
Chief, Review Branch  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
NIH, DHHS  
One Democracy Plaza  
6701 Democracy Blvd., Suite 800  
Bethesda, MD 20892-4872  
Telephone: 301-594-4953  
Email: [nesbittT@mail.nih.gov](mailto:nesbittT@mail.nih.gov)

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

Michael G. Morse  
Deputy Chief, Grants Management Branch  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
NIH/DHHS  
One Democracy Plaza  
6701 Democracy Blvd., Suite 800  
Bethesda, MD 20892-4872  
Phone: (301)594-3506

E-mail: [morsesem@mail.nih.gov](mailto:morsesem@mail.nih.gov)

## LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent that includes the following information:

- o Descriptive title of the proposed research
- o Name, address, and telephone number of the Principal Investigator
- o Names of other key personnel
- o Participating institutions
- o Number and title of this RFA

Although a letter of intent is not required, is not binding, 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 plan the review.

The letter of intent is to be sent by the date listed at the beginning of this document. The letter of intent should be sent to:

Teresa Nesbitt, D.V.M., Ph.D.  
Chief, Review Branch  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
NIH, DHHS  
One Democracy Plaza  
6701 Democracy Blvd., Suite 800  
Bethesda, MD 20892-4872  
Telephone: 301-594-4953  
Email: [nesbittT@mail.nih.gov](mailto:nesbittT@mail.nih.gov)

## SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a DUN and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number can be obtained by calling (866) 705-5711 or through the web site at [www.dunandbradstreet.com](http://www.dunandbradstreet.com). The DUNS number should be entered on line 11 of the face page of the PHS 398 form. The PHS 398 document 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](mailto:GrantsInfo@nih.gov).

**SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS:** 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>.

**USING THE RFA LABEL:** 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/labels.pdf>.

**SENDING AN APPLICATION TO THE NIH:** Submit a signed, typewritten original of the application, including the Checklist, 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 copies of the appendix material must be sent to:

Teresa Nesbitt, D.V.M., Ph.D.  
Chief, Review Branch  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
NIH, DHHS  
One Democracy Plaza  
6701 Democracy Blvd., Suite 800  
Bethesda, MD 20892-4872

**APPLICATION PROCESSING:** Applications must be received on or before the application receipt date listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within 8 weeks.

The Center for Scientific Review (CSR) 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, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be

submitted in response to an RFA, it is to be prepared as a NEW application. That is, the application for the RFA must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application.

## PEER REVIEW PROCESS

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by NIAMS. Incomplete applications will not be reviewed.

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 NIAMS in accordance with the review criteria stated below. As part of the initial merit review, all applications will:

- o Undergo 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 and assigned a priority score
- o Receive a written critique
- o Receive a second level review by the National Arthritis and Musculoskeletal and Skin Diseases 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 evaluate the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. The scientific review group will address and consider each of the following criteria in assigning the application's overall score, weighting them as appropriate for each application.

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

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.

**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?

**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?

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

**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)?

**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?

**ADDITIONAL REVIEW CRITERIA:** In addition to the above criteria, the following items will be considered in the determination of scientific merit and the priority score:

**PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK:** The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations, below).

**INCLUSION OF WOMEN, MINORITIES AND CHILDREN IN RESEARCH:** 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 in the sections on Federal Citations, below).

**CARE AND USE OF VERTEBRATE ANIMALS IN RESEARCH:** If vertebrate animals are to be used in the project, the five items described under Section f of the PHS 398 research grant application instructions (rev. 5/2001) will be assessed.

#### ADDITIONAL REVIEW CONSIDERATIONS

**BUDGET:** The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

#### RECEIPT AND REVIEW SCHEDULE

Letter of Intent Receipt Date: October 21, 2003

Application Receipt Date: November 18, 2003

Peer Review Date: February/March 2004

Council Review: June 2004  
Earliest Anticipated Start Date: July 2004

## AWARD CRITERIA

Award criteria that will be used to make award decisions include:

- o Scientific merit (as determined by peer review)
- o Availability of funds
- o Programmatic priorities.

## REQUIRED FEDERAL CITATIONS

**HUMAN SUBJECTS PROTECTION:** Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>

**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 "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](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>.

HUMAN EMBRYONIC STEM CELLS (hESC): Criteria for federal funding of research on hESCs can be found at <http://stemcells.nih.gov/index.asp> and at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html>.

Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see <http://escr.nih.gov>). It is the responsibility of the applicant to provide, in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s) to be used in the proposed research. Applications that do not provide this information will be returned without review.

#### 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](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.

## STANDARDS FOR PRIVACY OF INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION:

The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information", the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR). Those who must comply with the Privacy Rule (classified under the Rule as "covered entities") must do so by April 14, 2003 (with the exception of small health plans which have an extra year to comply).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (<http://www.hhs.gov/ocr/>) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html>.

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 RFA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at <http://www.healthypeople.gov/>.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance at <http://www.cfda.gov/> and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at <http://grants.nih.gov/grants/policy/policy.htm>

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](#)