

Full Text PA-96-022

## HUMAN MODELS AND MARKERS OF SKELETAL AGING

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National Institute of Diabetes and Digestive and Kidney Diseases

### PURPOSE

The National Institute on Aging (NIA), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Dental Research (NIDR) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) invite research grant applications to develop or refine models and markers using human bone, bone marrow or bone cell constituents which more accurately reflect those age-related and/or pathophysiological processes occurring within the mature human skeleton that lead to osteoporosis and other age-related skeletal diseases. It is expected that improved human models and markers of age-related changes in skeletal tissue structure and function will enhance the accuracy and reliability of diagnostic and prognostic capabilities and serve to expedite the development of more effective, targeted preventive and therapeutic strategies.

Model development and refinement should be conducted from the perspective of facilitating a) the identification of better prognostic indicators of the occurrence, progression, cessation or reversal of skeletal involution (due to aging, menopause, age-related morbidity, drugs); b) the identification

of age-related pathologies/co-morbidities contributing to compromises in peripheral, axial and craniofacial skeletal integrity; c) the prediction of response or non-response to various therapeutic agents and/or d) further epidemiologic studies of risk factors for age-related bone disease and bone loss and fracture outcomes.

## 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 PA, Human Models and Markers of Skeletal Aging is related to the priority area of osteoporosis. 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

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. Applications may be submitted by single institutions or by a consortia of institutions. Foreign institutions are not eligible for First Independent Research and Support and Transition (FIRST) awards (R29), but may submit applications for individual research project grants (R01): foreign applicants may also participate in laboratory or clinical programs through subcontract or consortium arrangements. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. If so, a letter of agreement from either the GCRC Program Director or Principal Investigator should be included with the application.

## MECHANISM OF SUPPORT

This program announcement will use the NIH investigator-initiated research project grant (R01) and FIRST (R29) award mechanisms. It is anticipated that the size of an award will vary due to

the nature and scope of the proposed research, with the R01 award ranging from \$150,000 to \$500,000 in total (direct plus indirect) costs per year.

## FUNDS AVAILABLE

Approximately \$900,000 from NIA and up to \$500,000 from NIAMS in total costs for the first year of funding will be made available in Fiscal Year 1997 to specifically fund applications submitted in response to this PA for the February/March 1996, June/July 1996 and October/November 1996 application receipt deadlines. An additional \$300,000 from NIA and \$200,000 from NIAMS will be made available in Fiscal Year 1998 to fund applications for this PA which are submitted by the February/March 1997 deadline. NIDR maintains a special interest in research focused on oral/craniofacial hard tissues, including related model systems and intends to fund 2-4 additional high quality applications in FY 1997. NIDDK also maintains an active interest in research questions related to the hormonal regulation of bone in health and disease and anticipates funding of 2-3 additional applications as funds warrant in FY97. This funding level is dependent on the receipt of a sufficient number of applications of high scientific merit. Although this program is provided for in the financial plans of the NIA, NIAMS, NIDR and NIDDK, the award of grants pursuant to this PA is contingent upon the availability of funds at the time the awards are made.

## RESEARCH OBJECTIVES

### Background

Our ability to predict, prevent, slow or reverse age-related bone loss and bone diseases such as osteoporosis is limited because so few studies have focused on cells and skeletal tissue from the aging human skeleton. Although osteoporosis and age-related diseases such as Paget's disease occur primarily in the mature, aging human skeleton, in vitro models used to study bone biology have consisted primarily of transformed cell lines from human or rodent osteosarcomas, or cell systems derived from fetal or neonatal rodent bone. In addition to marked differences in the chemical composition and macro- and microarchitectural organization of bone, other anomalies imposed by current models that reflect inappropriate age, species and other phenotypic characteristics limit the generalizability of putative biological mechanisms to those occurring in the human skeleton.

Appropriate model systems are needed to develop markers that are more sensitive and specific in predicting changes in bone mass, bone competence and fracture susceptibility. Significant improvements in techniques to assess the status of bone cell activity in the skeleton are

necessary to provide answers to key clinical questions such as 1) is a given individual currently losing bone?, 2) by which mechanisms is bone being lost? 3) at what anatomic site/compartments is bone being lost?, 4) at what rate is bone being lost?, 5) is a promising new treatment likely to be effective, and if so, for which patients and 6) if a treatment is initially effective, for how long will it continue to be effective?

Models and markers which better reflect the proliferative capability, differentiated function and qualitative features of bone cells in the mature human skeleton will facilitate improved techniques to assess the cellular and metabolic status of skeletal tissue. Such advances will further enhance the accuracy of diagnoses, prognoses and decision-making with respect to available and future treatment options and also facilitate the evaluation and targeting of potential new therapies (based on an understanding of how responses to these therapies are modified by age, gender, genetics and ethnicity). The acceleration of advances in bone biology and related fields as well as the development of many new promising technologies (such as transgenic animal models, in situ hybridization, immunocytochemistry and reverse transcriptase polymerase chain reaction (RT-PCR) in conjunction with histomorphometric, densitometric, qualitative, etc. techniques) provide improved capabilities to address these problems.

A Workshop on Human Models of Skeletal Aging was organized and sponsored by the NIA and the NIDR in Washington, D.C., on March 1-2, 1994. Its objective was to address methodological issues integral to facilitating clinically relevant studies on the causes and consequences of bone loss and osteoporosis at the cellular and tissue levels in the aging human skeleton. The proceedings of this Workshop have been published [*Calcif Tissue Int* (1995) 56(Suppl 1); pp S1-S56; eds., Gehron Robey P and Sherman S].

#### Research Goals and Scope

The purpose of this initiative is to stimulate studies to develop or refine and validate models and markers which more accurately reflect processes mediating aging or age-related skeletal diseases of the axial, peripheral and craniofacial skeleton, such as osteoporosis.

Research applications submitted in response to this PA must combine all three of the following components in the research plan proposed for the project period of the application (maximum five years):

1. Development of model systems for human skeletal aging and age-related disease, using human bone, bone marrow or other bone cell constituents.

2. Use of these model systems to define new markers for diagnosis and/or prognosis of age-related physiologic and pathologic changes, and/or prediction of responsiveness to specific therapies AND,
3. Validation of these models and markers against in vivo parameters of skeletal status such as changes in bone mass, bone strength, architecture, histomorphometric indices of bone turnover, or the occurrence of fractures.

The validation of models and markers against in vivo parameters of skeletal status is a required component for projects submitted in response to this PA. The validation component must include a plan to determine the extent to which proposed models and markers reflect changes due to age and/or age-related skeletal disease. Validation of markers should also include an assessment of their sensitivity, specificity, intra- and inter-individual variability (including effects of age, gender, and ethnicity).

Types of models and markers that might be developed include, but are not limited to:

- o Models of mature osteoblast, osteoclast, osteocyte, and bone lining cell function
- o Models of osteoprogenitor cell recruitment, proliferation, differentiation and function o Validated peripheral blood cell models (e.g. monocytes, CD 34+ cells) of osteoclast or osteoclast-like function
- o Markers of bone cell phenotype and stage of differentiation
- o Models that reflect embryonic origin (e.g., neuroectoderm versus mesoderm)
- o Models using bone from multiple anatomic (peripheral, axial and craniofacial) sites, and different types of bone, bone matrix, bone marrow and other cellular constituents; development of techniques requiring minimal amounts of skeletal material or constituents
- o Models derived from or synthesizing lamellar bone (of cortical or trabecular origin)
- o Models that can reconstitute the "BMU" (basic multicellular unit) which contains osteocytes, lining cells, osteoblasts, osteoclasts, vascular components, etc.

In vivo parameters that could be used to validate these models and markers include but are not limited to:

- o In vivo responses of bone (changes in bone mass, strength, etc) to regulatory factors (hormones, cytokines, etc.) and pharmacologic agents (measured by existing or new imaging techniques)
- o Bone cell or bone marrow progenitor proliferative capacity, morphology, surface markers, gene expression, and/or expression of differentiated function
- o Rates of bone formation and bone resorption (e.g., using histomorphometric techniques)
- o In vivo/in vitro or in situ spatial organization of cells and temporal sequence of events during the bone remodelling process
- o Qualitative and quantitative changes in organic and inorganic skeletal tissue components (structure, extent of mineralization, etc.)

Because age-related bone loss and osteoporosis are heterogeneous and multifactorial in nature, applicants are encouraged to adopt interdisciplinary approaches, establishing or strengthening interactions and integration of efforts between clinical and basic science investigators. Research teams should include, where possible, a diverse range of expertise in areas such as bone biology, molecular biology, bone densitometry, orthopedics, histomorphometry, endocrinology, geriatrics, epidemiology and biostatistics.

Because the current state of knowledge on skeletal aging and therapeutics in men is extremely limited, research proposing to include men (as well as women) as participants is strongly encouraged.

In their application(s), applicants are encouraged to request funds for one to two participants to meet annually in Bethesda, Maryland with investigators of similar projects. Program directors from participating institutes will coordinate these meetings which will provide the opportunity for principal investigators to share findings, discuss their work in progress and to raise cross-cutting methodological and scientific issues.

**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 new policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43) and supersedes and strengthens the previous policies (Concerning the Inclusion of Women in Study Populations, and Concerning the Inclusion of Minorities in Study Populations), which have been in effect since 1990. The new policy contains some provisions that are substantially different from the 1990 policies.

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 20, 1994 (FR 59 14508-14513) and reprinted in the NIH Guide for Grants and Contracts, Volume 23, Number 11, March 18, 1994.

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

#### APPLICATION PROCEDURES

Applications are to be submitted on the grant application form PHS 398 (rev. 5/95) and will be accepted at the standard application deadlines as indicated in the application kit. Applications kits are available at most institutional offices of sponsored research and may be obtained from the Grants Information Office, Office of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, email: [girg@drqpo.drg.nih.gov](mailto:girg@drqpo.drg.nih.gov). The title and number of this program announcement must be typed in Section 2 on the face page of the application.

Applications for the FIRST (R29) award must include at least three sealed letters of reference attached to the face page of the original application. FIRST (R29) award applications submitted without the required number of reference letters will be considered incomplete and will be returned without review.

The completed original application and five legible copies must be sent or delivered to:

DIVISION OF RESEARCH GRANTS

NATIONAL INSTITUTES OF HEALTH  
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC 7710  
BETHESDA, MD 20892-7710  
BETHESDA, MD 20817-7710 (for express/courier service)

#### 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 the standard 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. The review criteria to be used in the evaluation of applications submitted in response to this program announcement are:

- o Scientific, technical, or medical significance and originality of proposed research;
- o Appropriateness and adequacy of the experimental approach and methodology proposed to carry out the research;
- o Inclusion of all three required research components described under Research Goals and Scope
- o Qualifications and research experience of the Principal Investigator and staff, particularly, but not exclusively, in the area of the proposed research;
- o Availability of the resources necessary to perform the research;
- o Appropriateness of the proposed budget and duration in relation to the proposed research;
- o Adequacy of the provisions for the protection human subjects and safety of the research environment; and
- o Adequacy of plans to include both genders and minorities and their subgroups as appropriate for the scientific goals of the research.

Plans for the recruitment and retention of subjects will also be evaluated.

#### AWARD CRITERIA

Applications will compete for available funds with all other approved applications assigned to that IC. The following will be considered in making funding decisions:

- o Quality of the proposed project as determined by peer review;
- o Availability of funds; and
- o Program priority.

#### INQUIRIES

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

Direct inquiries regarding programmatic issues to:

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#### AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance Nos. 93.866, 93.846, 93.847 and 93.121. 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 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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