

Full Text PA-96-076

ANABOLIC HORMONES IN BONE: BASIC RESEARCH AND THERAPEUTIC POTENTIAL

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National Institute of Dental Research

National Institute on Aging

PURPOSE

The objective of this initiative is to elicit grant submissions, which focus on systemic hormones, local growth factors, and bone-active cytokines, which may have specific or generalized anabolic effects on bone. While the primary focus is on basic research, the long-term emphasis is on identifying mechanisms or processes related to hormone action with potential applicability as targets for therapeutic agents for the treatment of diseases, which adversely affect bone, including osteoporosis and primary hyperparathyroidism.

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, Anabolic Hormones in Bone: Basic Research and Therapeutic Potential, 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 Summary Report: Stock

No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-512-1800).

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. Foreign institutions are not eligible for the First Independent Research Support and Transition (FIRST) (R29) award. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as principal investigators.

MECHANISM OF SUPPORT

Support for this Program Announcement will be through the NIH research project grant (R01) and FIRST (R29) award mechanisms. Applicants will be responsible for the planning, direction, and execution of the proposed project. Applications submitted in response to this PA will compete for funds with other regular research project grant applications.

Applications 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.

The award of grants in response to this PA is also contingent upon the availability of funds. Awards will be administered under PHS grants policy as stated in the PHS Grants Policy Statement (rev. 4/94).

RESEARCH OBJECTIVES

Background

Diseases that affect bone, such as osteoporosis and primary hyperparathyroidism, result in gradual loss of bone. This osteopenia, or thinning of the bones, is a leading cause of fractures in the adult, and is particularly prevalent in women. Hormones are major regulators of bone mass and osteopenia may result from alterations in hormone action, such as loss of normal estrogen production in post-menopausal women, excessive production of parathyroid hormone (PTH) as in

primary hyperparathyroidism, or glucocorticoid excess as a consequence of chronic steroid use in immunosuppressive therapy. Other imbalances in local growth factors and/or bone-active cytokines resulting from a variety of conditions may also contribute to osteopenia. Limited clinical trials have been initiated to determine whether hormone replacement can mitigate or reverse the osteopenia associated with menopause, hypogonadism or primary hyperparathyroidism. To date therapeutic agents have been restricted to compounds which alter mineral content and/or molecular structure of bone (e.g., bisphosphonates) or alter hormonal balances (e.g., estrogen replacement therapy, calcitonin, vitamin D). Unintended or undesired side effects limit effectiveness of such agents.

This initiative stems from an NIDDK Workshop entitled: "Anabolic Hormones in Bone: Basic Research and Therapeutic Potential" which was held May 1-2, 1995 (see Margolis et al., Journal of Clinical Endocrinology and Metabolism 81 (3): 872-77, 1996), and co-sponsored by NIAMS and the NIH Office of Research on Women's Health. The workshop focused on hormones, growth factors, and cytokines which express positive, anabolic effects on bone mass, either directly or indirectly. The workshop identified several key issues essential to the development of agents with potential anabolic effects on bone, including: efficacy, mechanism of action, specificity, ease of use, and long-term benefit. This initiative is therefore designed to elicit grant submissions which focus on systemic hormones, local growth factors, and bone-active cytokines which may have specific or generalized anabolic effects on bone. While the primary focus is on basic research, the long-term emphasis should be on identifying mechanisms or processes associated with hormonal regulation of bone cell structure/function with potential applicability as therapeutic agents for the treatment of diseases which adversely affect bone, including osteoporosis and primary hyperparathyroidism.

Research Objectives and Scope

The major areas of interest and potential that have been identified relevant to this program announcement are the following:

- o The mechanism(s) of action of sex steroids, including estrogen, estrogen agonists, partial agonists, and agents with estrogen-like activity in bone; androgens and androgen-like agents which express positive, anabolic effects on bone.

- o Other members of the steroid/thyroid/retinoid superfamily, including vitamin D which may have positive effects on net bone mass.

- o Parathyroid hormone (PTH) and/or parathyroid hormone-related peptide (PTHrP) and agonists or partial agonists which express PTH- or PTHrP-like anabolic effects in bone.
- o Insulin-like growth factor I (IGF-I), IGF-I binding proteins, or any other component of the IGF axis which might help to safely express the positive effects of IGFs on bone.
- o Fibroblast growth factor(s) and their role(s) in bone/cartilage development and/or angiogenesis related to bone.
- o Members of the Bone Morphogenetic Protein family (e.g., TGFs).
- o Colony-stimulating factor-1.
- o Prostaglandins with effects on bone cells.
- o Interleukins, including those that have positive effects and agents which can oppose putative negative effects on bone.

This is by no means a complete listing of potentially important agents. The general focus should be on developing an understanding of the putative mechanism(s) of action of these agents with the goal of defining what aspect(s) of bone metabolism is/are affected and how anabolic actions may be achieved and sustained. The mission of the NIDDK is to provide broad fundamental and clinical research support for a spectrum of chronic and disabling diseases which affect bone, including osteoporosis and primary hyperparathyroidism. Applications for research focusing primarily or solely on craniofacial bone will be assigned to the National Institute of Dental Research. Applications that address changes in the levels of, and biologic responses to, these bone regulatory factors as a consequence of aging may be relevant to the National Institute on Aging.

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 subpopulations 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. Application 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: asknih@odrockm1.od.nih.gov.

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

Applications for the FIRST Award (R29) must include at least three sealed letters of reference attached to the face page of the original application. FIRST Award (R29) 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 (for express/courier service)

REVIEW CONSIDERATIONS

Applications will be assigned to initial review groups for review and to Institutes/Centers for possible funding on the basis of established Public Health Service referral guidelines. Applications that are complete will be evaluated for scientific and technical merit by an appropriate peer review group convened in accordance with NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate national advisory council or board.

Review Criteria

- 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 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 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.

The initial review group will also examine the provisions for the protection of human and animal subjects, the safety of the research environment.

- o availability of special opportunities for furthering research programs through the use of unusual talent resources, populations, or environmental conditions in other countries which are not readily available in the United States or which provide augmentation of existing U.S. resources.

AWARD CRITERIA

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

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

INQUIRIES

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

Direct inquiries regarding programmatic issues to:

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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.847 (NIDDK), 93.846 (NIAMS), 93.121 (NIDR), and 93.866 (NIA). Awards are 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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