

BONE ANABOLIC HORMONES, THEIR RECEPTORS AND SIGNAL TRANSDUCTION  
PATHWAYS

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National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

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

National Institute on Aging (NIA)

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

National Cancer Institute (NCI)

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

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

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

National Institute of Dental and Craniofacial Research (NIDCR)

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

THIS PA CONTAINS THE FOLLOWING INFORMATION

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PURPOSE OF THIS PA

The objective of this initiative is to elicit grant submissions that focus on systemic hormones, local growth factors and bone-active cytokines with potential bone anabolic effects. The signal transduction pathways recruited by the receptors of these hormones and growth factors are of particular interest. Although the primary focus is on basic research, the long-term objective is to identify potential targets of therapeutic value in the treatment of diseases that adversely affect bone including, but not limited to, osteoporosis due to loss of gonadal steroids, aging, use of glucocorticoids and immunosuppressive drugs, hyperparathyroidism, excessive thyroid hormone replacement, or tumor metastasis to bone.

## RESEARCH OBJECTIVES

### Background

Bone biology has benefited over the last decade from a tremendous explosion of information derived from analyses of mutations affecting skeletal development in man and mice. Indeed, studies on bone development have revealed roles for signaling through peptides such as PTHrP, hedgehog, Wnt, FGF, and BMP / TGF-beta family members; transcription factors from the Hox, Pax, Forkhead, NFkB, AP-1, Runx2/Cbfa1, and Osx families; and signal transducing molecules such as tyrosine kinases (e.g. c-src, c-fms), serine / threonine kinases, TRAFs and MAP kinases involved in bone cell fate determination, differentiation, and formation of mature bone. For example, analysis of Jansen's dyschondroplasia revealed the critical role of PTHrP signaling in skeletal development. Additionally, genetic analysis of families with osteoporosis-pseudoglioma syndrome and of kindreds with autosomal dominant high bone density have exposed the role of LDL receptor-related protein 5 (LRP5) and signaling in the Wnt pathway on regulation of bone mass and provide a new potential therapeutic avenue to treat osteopenia, or thinning of the bones.

It is clear that diseases that affect bone, such as osteoporosis and primary hyperparathyroidism, result in gradual net loss of bone mineral leading to osteopenia which is a leading cause of fractures in adults. Hormones are key regulators of bone mass and osteopenia may result from alterations in hormone action, such as loss of estrogen production in post-menopausal women or of androgens in older men, 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 (e.g. chronic inflammation, rheumatoid arthritis) may also contribute to osteopenia.

Research supported by previous Program Announcements (PA-96-076 and PA-00-017) and other initiatives revealed that growth factor signaling in developing and mature bone cells is key to maintaining proper mineral balance and peak bone mass. Results from a large clinical trial evaluating use of estrogen plus progestin in postmenopausal women demonstrated that the beneficial effects of hormone replacement therapy on bone are outweighed by its adverse effects on other organs (Writing group for the WHI, JAMA 288:321). A second study concluded that women using estrogen (alone) replacement therapy are at increased risk of developing ovarian cancer (Lacey et al. JAMA 288:334). The development and use of Selective Estrogen Receptor Modulators (SERMs) has served to partially offset these side effects while giving some degree of protection against post-menopausal bone loss. It is critical to understand the mechanisms underlying the beneficial effects of estrogen on bone in order to target new therapeutic agents that promote bone growth and integrity. In addition, other therapeutic agents have been developed that alter mineral content and/or molecular structure of bone (e.g., bisphosphonates), or that alter physiologic hormonal balances (e.g., calcitonin, vitamin D). The first truly bone anabolic therapeutic agent, intermittently administered PTH, may enter the market in the future, although the mechanism of PTH action in this context remains to be further elucidated.

This initiative is designed to elicit grant application submissions that focus on systemic hormones, growth factors and cytokines with bone anabolic effects and elucidation of the signal transduction pathways recruited by these factors. 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 emphasizing signal transduction in bone cells and their precursors, with potential applicability as therapeutic agents for the treatment of diseases that adversely affect bone, including osteoporosis, primary hyperparathyroidism, and tumor metastasis to bone. Potential therapeutic agents could mimic beneficial effects of anabolic hormones or antagonize harmful effects of hormones that cause bone loss.

#### 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, selective estrogen receptor modulators (SERMs), partial agonists, and agents with estrogen-like activity in bone; androgens and androgen-like agents (SARMs) which express positive, anabolic effects on bone.

- o The role of other members of the nuclear hormone receptor superfamily, including peroxisome proliferator-activated receptor (PPAR), and vitamin D in signaling in bone cells and their precursors.
  
- o Parathyroid hormone (PTH) and/or parathyroid hormone-related peptide (PTHrP) and agonists or partial agonists that express PTH- or PTHrP-like anabolic effects in bone and the mechanisms of signaling in developing, mature and aged bone.
  
- o LRP5, its interactions with Dickkopf-1 and the Wnt signaling pathways.
  
- o Insulin-like growth factor I (IGF-I), IGF-1 receptors, IGF-I binding proteins, or any other component of the IGF axis that signal in bone development and homeostasis.
  
- o Fibroblast growth factor(s) and their role(s) in bone/cartilage development and/or angiogenesis related to bone.
  
- o Members of the TGF / BMP family, their receptors and signal transducers such as members of the SMAD family.
  
- o Bone active cytokines including but not limited to Colony Stimulating Factors (e.g. CSF-1), RANKL / RANK / OPG axis, cytokine products of Th-1 and Th-2 T cells (e.g. interferons, TNFs, interleukins) which can modulate bone homeostasis, their receptors, and signaling pathways.
  
- o Novel transcription factors, such as Osx, Runx2/Cfba1, other Hox gene products, and their mechanisms of signaling in bone cells and their precursors.
  
- o Prostaglandins with effects on bone cells.
  
- o The roles of hormones, growth factors, cytokines or other factors and their receptors in craniofacial bone remodeling, damage and regeneration.
  
- o The roles of hormones, growth factors, cytokines in modulating the bone microenvironment and tumor metastasis to bone.

This is by no means a complete listing of potentially important hormones, growth factors, or cytokines. 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 signaling in

bone may be affected and how anabolic or other beneficial therapeutic actions may be achieved and sustained. Support for investigator initiated clinical trials designed to test the efficacy of novel anabolic factors or novel therapy regimens of clinically proven compounds may be sought through this initiative.

The NIDDK, NIAMS, and NIA share the mission to provide broad fundamental and clinical research support for a spectrum of chronic and disabling diseases that affect bone, including osteoporosis, hyperparathyroidism, and other diseases that result in bone loss. The NIDDK has a special interest in the endocrinology of bone, PTH / PTHrP signaling, the mechanism of action of calciotropic hormones, and gene regulation by steroid / nuclear hormone receptors. The NCI is interested in the identification and characterization of factors that affect tumor cell survival, growth and metastasis to bone. The NIDCR has special interest in research focusing on craniofacial bone.

#### MECHANISM(S) OF SUPPORT

This PA will use the NIH R01 and R21 award mechanism(s). As an applicant, you will be solely responsible for planning, directing, and executing the proposed project. Applicants without extensive preliminary data or who wish to explore innovative high risk/ high impact ideas that are scientifically sound are encouraged to submit applications for this PA using the R21, exploratory / developmental grant mechanism. Investigators are encouraged to seek continued support after completing an exploratory / developmental grant project through a research project grant (R01). Please see the "Submitting an Application" section for more details. Applicants for the R21 must limit their request to \$100,000 direct costs per year and are limited to two years of requested support.

This PA uses just-in-time concepts. It also uses the modular as well as the non-modular budgeting formats (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 format. Otherwise follow the instructions for non-modular research grant applications.

#### ELIGIBLE INSTITUTIONS

You may submit (an) application(s) 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

## 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 your inquiries concerning this PA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into two areas: scientific/research and financial or grants management issues:

- o Direct your questions about scientific/research issues to:

Mehrdad Tondravi, Ph.D.  
Program Director for Bone & Mineral and Steroid Metabolism  
Division of Diabetes, Endocrinology, and Metabolic Diseases  
National Institute of Diabetes and Digestive and Kidney Diseases  
6707 Democracy Blvd., Room 603  
Bethesda, MD 20892-5460  
Telephone: (301) 451-9871  
FAX: (301) 435-6047  
E-mail: [mt270t@nih.gov](mailto:mt270t@nih.gov)

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National Institute on Aging  
7201 Wisconsin Avenue, Suite 2C231  
Bethesda, MD 20892-9205  
Telephone: (301) 496-6402  
FAX: (301) 402-0010  
E-mail: [carringtonj@nia.nih.gov](mailto:carringtonj@nia.nih.gov)

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Rockville, MD 20892  
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FAX: (301) 480-0864  
E-mail: [mohals@mail.nih.gov](mailto:mohals@mail.nih.gov)

William Sharrock, Ph.D.  
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Telephone: (301) 594-5055  
FAX: (301) 480-4543  
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Guo H. Zhang, Ph.D., M.P.H.  
Division of Basic and Translational Sciences  
National Institute of Dental and Craniofacial Research  
45 Center Drive, Building 45, Room 4An18B  
Bethesda, MD 20892  
Telephone: (301) 594-0618  
FAX: (301) 480-8318  
E-mail: [Zhanggu@mail.nih.gov](mailto:Zhanggu@mail.nih.gov)

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

Florence Danshes  
Senior Grants Management Specialist  
Grants Management Branch, DEA  
National Institute of Diabetes and Digestive and Kidney Diseases  
6707 Democracy Blvd., 734  
Bethesda, MD 20892  
Telephone: (301) 594-8861

FAX: (301) 480-3504

E-mail: [fd39j@nih.gov](mailto:fd39j@nih.gov)

Linda Whipp

Grants and Contracts Management Office

National Institute on Aging

7201 Wisconsin Avenue, Suite 2N212

Bethesda, MD 20892-9205

Telephone: (301) 496-1472

FAX: (301) 402-3672

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

Bill Wells

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Rockville, MD 20892

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FAX: (301) 496-8606

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

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Fax: (301) 480-8301

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

## SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 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).

APPLICATION RECEIPT DATES: Applications submitted in response to this program announcement will be accepted at the standard application deadlines, which are available at <http://grants.nih.gov/grants/dates.htm>, and include February 1, June 1, and October 1. These application deadlines are also indicated in the PHS 398 application kit.

SPECIFIC REQUIREMENTS FOR R21 APPLICATIONS: All application instructions outlined in the PHS 398 application kit are to be followed, with the following requirements for R21 applications:

1. R21 applications will use the "MODULAR GRANT" and "JUST-IN-TIME" concepts, with direct costs requested in \$25,000 modules, up to the total direct costs limit of \$100,000 per year.
2. Although preliminary data are not required for an R21 application, they may be included.
3. Sections a-d of the Research Plan of the R21 application may not exceed 15 pages, including tables and figures.
4. R21 appendix materials should be limited, as is consistent with the exploratory nature of the R21 mechanism, and should not be used to circumvent the page limit for the research plan. Copies of appendix material will only be provided to the primary reviewers of the application and will not be reproduced for wider distribution. The following materials may be included in the appendix:

- o Up to five publications, including manuscripts (submitted or accepted for publication), abstracts, patents, or other printed materials directly relevant to the project. These may be stapled as sets.

- o Surveys, questionnaires, data collection instruments, and clinical protocols. These may be stapled as sets.
- o Original glossy photographs or color images of gels, micrographs, etc., provided that a photocopy (may be reduced in size) is also included within the 15 page limit of items a-d of the research plan

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>.

SPECIFIC INSTRUCTIONS FOR APPLICATIONS REQUESTING \$500,000 OR MORE PER YEAR:

Applications requesting \$500,000 or more in direct costs for any year must include a cover letter identifying the NIH staff member within one of NIH institutes or centers who has agreed to accept assignment of the application.

Applicants requesting more than \$500,000 must carry out the following steps:

- 1) Contact the IC program staff at least 6 weeks before submitting the application, i.e., as you are developing plans for the study;
- 2) Obtain agreement from the IC staff that the IC will accept your application for consideration for award; and,
- 3) Identify, in a cover letter sent with the application, the staff member and IC who agreed to accept assignment of the application.

This policy applies to all investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended or revised version of these grant application types. Additional information on this policy is available in the NIH Guide for Grants and Contracts, October 19, 2001 at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-004.html>.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the checklist, and five 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)

APPLICATION PROCESSING: Applications must be received by or mailed on or before the receipt dates described at <http://grants.nih.gov/grants/funding/submissionschedule.htm>. The CSR will not accept any application in response to this PA that is essentially the same as one 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 a substantial revision of an application already reviewed, but such application must include an Introduction addressing the previous critique.

#### PEER REVIEW PROCESS

Applications submitted for this PA will be assigned on the basis of established PHS referral guidelines. An appropriate scientific review group convened in accordance with the standard NIH peer review procedures (<http://www.csr.nih.gov/refrev.htm>) will evaluate applications for scientific and technical merit.

As part of the initial merit review, all applications will:

- o Receive a written critique
- o Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score
- o Receive a second level review by the appropriate national advisory council or board

#### 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 your application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals:

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

The scientific review group will address and consider each of these criteria in assigning your application's overall score, weighting them as appropriate for each application. Your 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, you may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

(1) SIGNIFICANCE: Does your study address an important problem? If the aims of your application are achieved, how do they advance scientific knowledge? 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? Do you acknowledge potential problem areas and consider alternative tactics?

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

(4) INVESTIGATOR: Are you appropriately trained and well suited to carry out this work? Is the work proposed appropriate to your experience level as the principal investigator and to that of other researchers (if any)?

(5) ENVIRONMENT: Does the scientific environment in which your 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, your application will also be reviewed with respect to the following:

PROTECTIONS: The adequacy of the proposed protection for humans, animals, or the environment, to the extent they may be adversely affected by the project proposed in the application.

INCLUSION: 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 included in the section on Federal Citations, below)

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

#### AWARD CRITERIA

Applications submitted in response to a PA will compete for available funds with all other recommended applications. 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 Relevance to program priorities

#### REQUIRED FEDERAL CITATIONS

MONITORING PLAN AND DATA SAFETY AND MONITORING BOARD: Research components involving Phase I and II clinical trials must include provisions for assessment of patient eligibility and status, rigorous data management, quality assurance, and auditing procedures. In addition, it is NIH policy that all clinical trials require data and safety monitoring, with the method and degree of monitoring being commensurate with the risks (NIH Policy for Data Safety and Monitoring, NIH Guide for Grants and Contracts, June 12, 1998: <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>).

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 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](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://grants.nih.gov/grants/stem\\_cells.htm](http://grants.nih.gov/grants/stem_cells.htm) 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 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.

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

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance No. 93.847 for NIDDK, 93.866 for NIA, 93.121 for NIDCR, 93.396 for NCI, and 93.846 for NIAMS and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies described at <http://grants.nih.gov/grants/policy/policy.htm> and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92.

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.

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