

Full Text PA-97-001

STEROID RECEPTOR STRUCTURE: FUNCTIONAL CONSIDERATIONS

NIH GUIDE, Volume 25, Number 34, October 11, 1996

PA NUMBER: PA-97-001

P.T. 34

Keywords:

Receptors

Steroids

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Arthritis and Musculoskeletal and Skin Diseases National Institute on Aging

PURPOSE

The objective of this initiative is to elicit grant submissions that focus on integrating structural with functional information about the receptors in the steroid/thyroid/retinoid superfamily, including the orphan receptors for which no known ligands have been identified.

Also referred to as nuclear receptors, the identification and characterization of the receptors for many of these hormones has revealed several examples of mutations in key domains or alterations in function which have been linked to human diseases, including vitamin D-dependent rickets, thyroid hormone resistance, and androgen resistance syndrome. In addition, hormones and their receptors in this large superfamily have been linked to breast, prostate (and other) cancers, osteoporosis, obesity, diabetes, and other diseases or disorders. Finally, agonists and/or antagonists of steroid/thyroid/retinoid hormones may have clinical utility for the prevention or treatment of diseases with significant health relevance to women, including breast cancer and osteoporosis.

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, Steroid Receptor Structure: Functional Considerations, 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 First Independent Research Support and Transition (FIRST) (R29) awards. 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. Applicants will be responsible for the planning, direction, and execution of the proposed project. 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).

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.

RESEARCH OBJECTIVES

Background

The receptors for hormones in the steroid/thyroid/retinoid supergene family are transcription factors which bind to target sequences in the regulatory regions of hormone-sensitive genes to enhance or suppress their transcription. These receptors have evolutionarily conserved similarities in a series of discrete structural domains, including a ligand binding domain (LBD), a DNA binding domain (DBD), a dimerization domain, and one or more trans-activation domain(s) (AF-1/AF-2). While most members of this family have well characterized ligands, others have no known ligand(s). These "orphan" receptors often have domains with sequences that resemble LBDs suggesting that ligands do exist. In other instances, the absence of consensus LBDs suggests that ligand binding is not a requisite of function. Upon ligand binding most of the receptors in this supergene family form either homo- or hetero-dimers, which bind to discrete regulatory regions of the promoters of target genes called hormone response elements (HRE). There is also a subset of members of the family which bind DNA as monomers. Binding to DNA may occur with or without ligand and may result in repression or enhancement of gene expression in a cell/promoter context. More recently it has become evident that additional nuclear accessory proteins are required to effect receptor-dependent repression or activation of gene expression. The structure of the receptor, the HRE, and the presence/absence of accessory proteins all represent key determinants of the final effect on expression of target genes. New information is developing at a rapid pace delineating the three-dimensional structure of these receptors. To date, the x-ray crystallographic structure has been solved for the LBD of the thyroid receptor, the retinoic X receptor (RXR)gamma, and the peroxisome proliferator-activated receptor (PPAR)gamma. Similarities in conserved regions of other receptors, including the estrogen receptor and the vitamin D receptor, have allowed models to be created which putatively assign key amino acid residues roles in ligand binding and regulation of transcription activation domains. Such information is increasingly important as a guide for the development of compounds which can act as full or partial agonists, or antagonists in a therapeutic context. Therefore, it is important to integrate emerging and developing information about receptor structure with function of these receptors in cell and promoter-specific contexts.

The long-term goal of this initiative is to increase basic understanding of the receptors in this hormone superfamily to allow for development of specific analogs, partial agonists, or antagonists with clinical significance in the treatment of disease (e.g., osteoporosis, obesity, breast or prostate cancer). This initiative is therefore designed to elicit grant submissions which focus on the structure of steroid/thyroid/retinoid (nuclear) receptors, including the orphan receptors for

which no known ligand has been identified, and the implications of this structural information for understanding function.

Research Objectives and Scope

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

- o Effects of binding of agonists/antagonists to steroid receptors on structure/function of the receptor
- o Role(s) of cytosolic accessory proteins in three-dimensional folding, subcellular processing, activation/inactivation of steroid receptors
- o Role(s) of nuclear accessory proteins in mediating proper interaction(s) of liganded or unliganded nuclear receptors with hormone response elements and/or components of the transcriptional apparatus
- o Effects of structural or mutational alterations in receptor structure on cell/promoter specificity of the receptor: effects of homo- or hetero-dimerization and/or HRE spacing and DNA bending on transactivation
- o Components of the structure of steroid receptors and/or the HRE which have a role in determining the cell, tissue, or promoter specificity of function

While these areas of interest are representative of the intended scope, the general focus should be on developing an understanding and integration of structure and function of steroid/thyroid/retinoid receptors. Applications addressing changes in the structure and function of these receptors as a direct 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, or 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 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 assigned to the NIDDK, NIAMS, or NIA. 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:

Ronald N. Margolis, Ph.D.
Endocrinology Section
National Institute of Diabetes and Digestive and Kidney Diseases
Building 45, Room 5AN-12J
45 Center Drive
Bethesda, MD 20892-6600
Telephone: (301) 594-8819
FAX: (301) 480-3503
Email: rm76f@nih.gov

William Sharrock, Ph.D.
Bone Biology Program
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Natcher Building, Room 5AS-43E
45 Center Drive, MSC 4500
Bethesda, MD 20892-6500
Telephone: (301) 594-5055
FAX: (301) 480-4543

Email: william_sharrock@nih.gov

Frank Bellino, PhD
Biology of Aging Program
National Institute on Aging
Gateway Building, Suite 2C231
Bethesda, MD 20892-9205
Telephone: (301) 496-6402
FAX: (301) 402-0010
Email: bellinof@gw.nia.nih.gov

Direct inquiries regarding fiscal and administrative matters to:

Kim Law
Grants Management Specialist
National Institute of Diabetes and Digestive and Kidney Diseases
Building 45, Room 6AS-49A
45 Center Drive
BETHESDA, MD 20892-6600
Telephone: (301) 594-8869

Vicki Maurer
Grants Management Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Natcher Building, Room 5AS-49A
45 Center Drive, MSC 4500
Bethesda, MD 20892-6500
Telephone: (301) 594-3504
FAX: (301) 480-4543
Email: vicki_maurer@nih.gov

Robert Pike
Grants and Contracts Management Office
National Institute on Aging
Gateway Building, Suite 2N212
Bethesda, MD 28092-9205
Telephone: (301) 496-1472

FAX: (301) 402-3672

Email: pikeb@gw.nia.nih.gov

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.847 (NIDDK), No. 93.846 (NIAMS), and No. 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.

[Return to PA Index](#)

[Return to NIH Guide Main Index](#)