

EMERGING TECHNOLOGIES FOR THE STUDY OF REPRODUCTIVE NEUROENDOCRINOLOGY

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National Institute of Child Health and Human Development (NICHD)
(<http://www.nichd.nih.gov/>)

National Institute of Neurological Disorders and Stroke (NINDS)
(<http://www.ninds.nih.gov/>)

CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBERS: 93.864 AND 93.853

THIS PA CONTAINS THE FOLLOWING INFORMATION

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PURPOSE OF THE PA

The National Institute of Child Health and Human Development (NICHD) and the National Institute of Neurological Disorders and Stroke (NINDS) invite applications dealing with nervous system control of reproduction. The purpose of this PA is to stimulate the development of new technologies and the application of existing innovative technologies to answer questions regarding the neuroendocrine control of reproduction that, up to this point, could not be answered due to limitations in technology. Answers to these questions are particularly critical for human reproduction given the increased evidence for altered neuroendocrine function as an etiological underpinning for certain reproductive diseases and disorders.

RESEARCH OBJECTIVES

Background

Dubbed as "the Decade of the Brain," the 1990s saw an explosion of innovative technologies to probe neurological function. Of significance was the development of new non-invasive procedures to monitor real time neural activity such as functional magnetic resonance imaging. This decade also saw the emergence of nanoscience and accompanying nanotechnologies, including the availability of powerful imaging techniques with cellular and subcellular resolution. Coupled with the development of profiling strategies for genomes and proteomes, and laser capture microdissection procedures, the use of non-invasive and invasive procedures offers the opportunity to identify functional

changes in discrete brain regions and the functionally related genes that may be responsible for the changes in neural cell activity. Importantly, non-invasive imaging approaches allow monitoring of real-time brain activity in the human. As such, this PA expresses the interest of NICHD and NINDS to support research in the area of reproductive neuroendocrinology using these new, and yet to be developed, technologies with particular emphasis on human applications.

Research Scope

Applications submitted in response to this PA may propose hypothesis-driven, discovery-driven or developmental research. Projects deemed responsive to this PA include, but are not limited to: 1) basic, applied and clinical research proposals that seek to investigate the neuroendocrine control of reproduction using innovative invasive or non-invasive approaches, and 2) projects that propose to develop new technologies to monitor neuroendocrine activity, particularly non-invasive approaches that have the potential for use in humans.

Important areas of neuroendocrine regulation of reproductive function of interest to NICHD that may be addressed by these technologies include, but are not limited to:

- o Non-invasive, high-resolution brain imaging techniques to assess in vivo changes in hypothalamic reproductive function;
- o Electrophysiological, cell imaging and molecular techniques for the in situ assessment of the activity of gonadotropin-releasing hormone (GnRH), and of other neurons involved in the control of GnRH neuronal function;
- o Genomic and proteomic approaches to identify and characterize global changes in gene and protein expression that occur in the neuroendocrine brain and pituitary gland in relation to key physiological events of reproductive function;
- o Laser capture microdissection approaches coupled to gene profiling technology to define the existence of cell-specific changes in gene expression in phenotypically identified cells within the neuroendocrine brain and pituitary gland;
- o Genomic and genetic approaches to identify novel genes and gene networks involved in the neuroendocrine control of reproduction;
- o Nanotechnology to identify the sub-cellular mechanisms underlying the transsynaptic and glial control of GnRH neuronal function;
- o Combination of the above-mentioned approaches coupled with morphological techniques to identify key changes in synaptic remodeling that may occur in the hypothalamus during reproductive life;
- o Identification of molecules involved in neuron-neuron and glia-neuron adhesiveness and cell-cell signaling within the neuroendocrine brain that are important for control of reproduction.

The NINDS encourages the behavioral neuroendocrinology community to highlight the new research directions identified in this PA. NINDS is

particularly interested in the application of innovative technologies to study neural control of reproductive function in clinical populations and animal models of neurological disorders where reproductive function is compromised.

MECHANISM OF SUPPORT

This PA will use the NIH Research Project Grant (R01) and Exploratory/Developmental Grant (R21) award mechanisms. As an applicant you will be solely responsible for planning, directing, and executing the proposed project.

Applications for R21 exploratory/developmental grants should be submitted with the intent to: 1) generate pilot data to assess the feasibility of a novel avenue of investigation; 2) propose high-risk experiments that could lead to a breakthrough discovery; or 3) develop new technologies that can be utilized for the study of reproductive neuroendocrinology. R21 applications may not request more than \$125,000 in direct costs per year for up to two years. Applicants are encouraged to contact program staff for advice about choosing the appropriate grant mechanism. These grants are not renewable.

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. 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.

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

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 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:

Louis V. DePaolo, Ph.D.
Reproductive Sciences Branch
National Institute of Child Health and Human Development
6100 Executive Boulevard, 8B01H, MSC 7510
Bethesda, MD 20892-7510
Telephone: (301) 435-6970
Email: depaolol@mail.nih.gov

OR

Emmeline Edwards, Ph.D.
Systems and Cognitive Neuroscience
National Institute of Neurological Disorders and Stroke
6001 Executive Boulevard, Room 2109
Bethesda, MD 20892
Telephone: (301) 496-9964
Email: ee48r@nih.gov

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

Mary Ellen Colvin
Grants Management Branch
National Institute of Child Health and Human Development
6100 Executive Boulevard, 8A17, MSC 7510
Bethesda, MD 20892-7510
Telephone: (301) 496-1304
Fax: (301) 402-0915
Email: colvinm@mail.nih.gov

OR

Aaron Kinchen
Grants Management Branch
National Institute of Neurological Disorders and Stroke
6001 Executive Boulevard, Room 3271
Bethesda, MD 20892
Telephone: (301) 496-7386
Email: ak284o@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.

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>. Application deadlines are also indicated in the PHS 398 application kit.

SPECIFIC INSTRUCTIONS FOR SUBMISSION OF R21 APPLICATIONS: The Research Plan section of the application for R21 Exploratory/Developmental applications may not exceed 15 pages.

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:

Contact the IC program staff at least six 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 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.

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

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 the 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 the application's overall score, weighting them as appropriate for each application. 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 will be assessed. 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 CONSIDERATIONS

DATA SHARING: The adequacy of the proposed plan to share data.

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

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.

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 is available at 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>.

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.

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 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.