NIH GUIDE

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The NIH Guide announces scientific initiatives and provides policy and administrative information to individuals and organizations who need to be kept informed of opportunities, requirements, and changes in extramural programs administered by the National Institutes of Health.

Vol. 19, No. 40
November 9, 1990

NOTICES OF AVAILABILITY (RFPs AND RFAs)

ONGOING PROGRAM ANNOUNCEMENTS

A REPOSITORY OF MOUSE MODELS FOR CYTOGENETIC DISORDERS

RFP AVAILABLE: NICHD-CRMC-91-01

P.T. 34; K.W. 1002002, 1002019

National Institute of Child Health and Human Development

The National Institute of Child Health and Human Development (NICHD) is seeking proposals from organizations to continue developing a repository for the production, maintenance, and distribution of aneuploid mice with a primary emphasis on trisomy sixteen (16). The organization will be responsible for refining methodologies to produce segmental (partial) trisomies and improving the production of chimeric mice with a trisomic 16 component. The selected source will be required to breed various strains of mice to produce trisomic or monosomic embryos with emphasis on chromosome 16, continue developing the process of freezing, rescuing, and reimplanting embryos into pseudo-pregnant mice, continue development of methods to improve the production of chimeric mice with a trisomic component, and distribute the mice to requestors.

The Request for Proposals (RFP) will be issued on or about November 1, 1990. Proposals will be due January 15, 1991, no later than 4:00 p.m. (Local Time). Organizations desiring a copy of the solicitation may send their written requests to the following address:

Mrs. Dorothy McKelvin
NIH, NICHD, OGC, CMB
9000 Rockville Pike
Executive Plaza North, Room 515
Bethesda, MD 20892
Telephone: (301) 496-4611

All requests must cite the RFP number above and include two self-addressed mailing labels. All sources who consider themselves qualified are encouraged to submit proposals. The Institute plans to make one award from this solicitation.

INSULIN, INSULIN RESISTANCE, HYPERGLYCEMIA AND CARDIOVASCULAR DISEASE: FIELD CENTERS, COORDINATING CENTER AND CENTRAL LABORATORIES

RFA AVAILABLE: HL-91-03-P

P.T. 34; K.W. 0715075, 0715040, 0755018

National Heart, Lung, and Blood Institute

Application Receipt Date: April 5, 1991

The Clinical and Genetic Epidemiology Branch of the Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute (NHLBI), announces the availability of a Request for Applications (RFA) on the above subject.

This program will support epidemiologic and clinical investigators and supporting staff to collaboratively plan and execute a study to assess the relationships of insulin and insulin resistance to cardiovascular disease (CVD) and its risk factors over a range of glucose tolerance from normal to overt diabetes. Major aims of the study are to employ a common protocol to assess the associations of increasing concentrations of glucose and changing levels of insulin and insulin resistance with levels of other CVD risk factors and prevalence of CVD, using a population-derived, stratified sample so there are adequate numbers to assess variations in individual CVD risk factors and evidence of disease over a range of glucose tolerance from normal through overt diabetes. This survey will provide insight into the reasons for the changing risk of CVD at increasing glucose levels and may help to explain the apparent difference in the contribution of hyperglycemia to the risk of CVD in men and women.

In view of the size of this study and the anticipation that some needs will not be identified until the protocol is developed, central functions of the collaborative activity, a Coordinating Center and a Central Laboratory will be performed by or under the direction of one or more of the examination centers. Each Field Center applicant is invited to apply to serve as one or more of these support units for the study. A separate application should be submitted

for each support unit. Applicants should discuss the special functions of any proposed support activity, including methodology and quality control assessment, and provide an estimated time for the work to be completed.

Investigators should be aware that NIH requires applicants to give added attention, where feasible and appropriate, to the inclusion of minorities and women in study populations. Gender and minority population differences must be noted and analyzed whenever possible. If minorities and/or women are not included in a given study, a clear reason for their exclusion must be provided. Merely including an arbitrary number of minority group and women participants in a given study is insufficient to guarantee generalization of results.

Interested institutions may request copies of the RFA. Requests for copies of the RFA should be addressed to:

Peter J. Savage, M.D.
Clinical and Genetic Epidemiology Branch
Division of Epidemiology and Clinical Applications
National Heart, Lung, and Blood Institute
Federal Building, Room 300
7550 Wisconsin Ave.
Bethesda, MD 20892
Telephone: (301) 496-4333

ALZHEIMER'S DISEASE CENTER CORE GRANTS

RFA AVAILABLE: AG-91-02

P.T. 04; K.W. 0715180, 0710010, 0715138

National Institute on Aging

Letter of Intent Receipt Date: December 3, 1990
Application Receipt Date: February 11, 1991

BACKGROUND

The National Institute on Aging (NIA) is inviting applications from qualified institutions for Alzheimer's Disease Center Core grants (ADCC), which are designed to serve as shared research resources, to facilitate research in Alzheimer's disease (AD). The NIA currently supports five ADCCs. This one-time solicitation is designed to increase the number of ADCCs. The NIA Alzheimer's Disease Centers program is authorized by the Public Health Service Act, Section 445.

An ADCC will provide support for cores, which are shared resources, to be used by ongoing and to-be-developed research projects. An ADCC is required to have an administrative, clinical, neuropathological, and education and information transfer core. Additional cores can be proposed. Each ADCC will fund two pilot research projects.

ELIGIBILITY

Institutions eligible for Center Core Grants (P30s) are those at which there are (1) at least three prinicipal investigators with any PHS agency grant or comparable peer-reviewed research project (including those funded by State governments or private foundations) related to Alzheimer's disease, each with at least two years of committed support remaining at the time of application; or (2) one or more program projects (P01) grants related to AD, which also have at least two years of committed support remaining. Institutions that can demonstrate the ability to launch such a research effort are also eligible.

MECHANISM OF SUPPORT

The support mechanism for this program will be the Center Core Grant (P30). Investigators may request up to five years of support. The intent is to fund up to five ADCC grants in Fiscal Year 1991. The total costs (direct plus indirect) for each ADCC are limited to $600,000 for the first year.

REVIEW PROCEDURES

In preparing proposals, instructions for PHS Form 398 (10/88 revision) and specific supplemental guidelines available from NIA program staff should be used. Proposals judged by staff to be nonresponsive to the RFA will be administratively withdrawn and returned to the applicant without review. Responsive proposals may then receive a preliminary review by a subcommittee

of the review panel to establish those applications deemed to be competitive. Those judged noncompetitive will be so designated, and an abbreviated summary statement noting the major areas of concern will be sent to the principal investigator. Applications judged to be competitive will be given full review. Following review by the initial review group, the applications will be considered by the National Advisory Council on Aging.

NIH requires applicants for grants to give added attention (where feasible and appropriate) to the inclusion of women and minorities in study populations and as units of analysis. If minorities and women are not included in a study population, a clear and convincing rationale for their exclusion must be provided.

Although not a prerequisite for applying, potential applicants are encouraged to submit to the Chief, Dementias of Aging, Neuroscience and Neuropsychology of Aging Program (NNA), at the address indicated below, a non-binding letter of intent to apply no later than December 3, 1990. The letter of intent should include a brief descriptive title, the names of the principal investigator(s) and other key investigators, and any other participating institutions. Applications must be received by February 11, 1991 for an earliest start date of September 30, 1991. Applicants are strongly encouraged to obtain the complete Request for Applications (RFA) and supplemental information and to discuss their plans with and direct any other inquirires to:

Chief, Dementias of Aging
NNA, NIA, NIH
Building 31, Room 5C35
9000 Rockville Pike
Bethesda, MD 20892
Telephone: (301) 496-9350
FAX: (301) 496-1494

MECHANISMS OF RESTENOSIS AFTER CORONARY ANGIOPLASTY

RFA AVAILABLE: HL-91-02-H

P.T. 34; K.W. 0715040, 1002004, 0760020

National Heart, Lung, and Blood Institute

Application Receipt Date: March 18, 1991

The Division of Heart and Vascular Diseases of the National Heart, Lung, and Blood Institute, NIH, announces the availability of a Request for Applications (RFA) on the above mentioned topic. Applicants may request up to five years of support for studies of the restenosis after coronary angioplasty. Investigations may focus on the roles of growth factors, cell-cell communications, cell adhesion molecules, and on other factors involved in regulation of cellular and metabolic responses to mechanical revascularization.

Investigators should be aware that NIH requires applicants to give added attention, where feasible and appropriate, to the inclusion of minorities and women in study populations. Gender and minority population differences must be noted and analyzed whenever possible. If minorities and/or women are not included in a given study, a clear reason for their exclusion must be provided. Merely including an arbitrary number of minority group and women participants in a given study is insufficient to guarantee generalization of results.

Potential applicants are advised to obtain the full RFA announcement from:

George Sopko, M.D., M.P.H.
Cardiac Diseases Branch
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
Federal Building, Room 3C06
Bethesda, MD 20892
Telephone: (301) 496-1081

COLLABORATIVE RESEARCH PLANNING GRANT - DIABETES IN AMERICAN INDIANS AND ALASKA NATIVES

RFA AVAILABLE: DK-91-01

P.T. 34, FE; K.W. 0715075, 0755030, 0765033, 0745070, 0745027

National Institute of Diabetes and Digestive and Kidney Diseases

Letter of Intent Receipt Date: December 15, 1990
Application Receipt Date: February 15, 1991

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Indian Health Service (IHS) have initiated a joint program on Diabetes in American Indians and Alaska Natives to help improve the health status of these populations. In this Request for Applications (RFA), NIDDK invites applications for Collaborative Research Planning Grants to support the development of plans for collaborative research projects that address critical questions related specifically to the etiology, pathogenesis, diagnosis, treatment, cure, and prevention of diabetes mellitus and its complications in American Indians and Alaska Natives.

Collaborative research studies proposed in response to this RFA may involve basic biomedical research, clinical research, behavioral research, education research, clinical trials, and epidemiologic research. Accordingly, the applicant research team should include individuals with the appropriate scientific, medical, and sociocultural expertise to pursue the proposed research project. In this regard, special consideration should be given to including team members with demonstrated access, knowledge, and cultural sensitivity to the specified study population.

This RFA is a one-time solicitation by NIDDK for applications for Collaborative Research Planning Grants (R21) to help support the unique short-term needs of investigators planning research studies related to diabetes in American Indians and Alaska Natives. The award of these Collaborative Research Planning Grants will be followed within approximately one year by an RFA for investigator-initiated research project grant applications (R01) related to this same program area.

Teams of applicants are encouraged that could include universities, public health departments, IHS Hospitals, voluntary organizations, health clinics, and federally recognized Indian tribe or tribal organizations as defined in P.L. 93-638 and amended by P.L. 100-472, etc., or combinations thereof. Among a team of applicants, one institution must be proposed as the lead organization to serve as the Grantee Institution and assume responsibility for the fiscal and programmatic conduct of the project.

Applicants are encouraged to submit and describe their own ideas on how best to meet the objective of this RFA. Applications will be judged primarily on (1) the likelihood that the new knowledge that may be gained will subsequently help to reduce the burden of diabetes and its complications on the health status of American Indians and Alaska Natives; (2) the potential scientific and technical merit of the proposed project including the significance of the scientific question(s), rationale, appropriateness of the proposed planning process, consideration of appropriate ethical issues, and availability of preliminary data; (3) the agreement of a suitable American Indian population to participate in planning the proposed study, and potential to establish collaboration with the tribal groups and other agencies involved in health care of the selected populations; and (4) the qualifications and experience of the proposed investigators.

Prospective applicants are requested to submit a letter of intent by December 15, 1990, that includes a descriptive title of the proposed research, the name, telephone number and mailing address of the Principal Investigator, the names of other key personnel, the name of the applicant institution and other collaborating entities, and the number and title of this RFA.

This letter of intent should be sent to:

Dr. Robert D. Hammond
Chief, Review Branch
Division of Extramural Activities
National Institute of Diabetes and Digestive and Kidney Diseases, NIH
Westwood Building, Room 406
Bethesda, MD 20892

Requests for the full text of this RFA and inquiries should be directed to the following NIDDK Program Staff:

Dr. Robert E. Silverman
Chief, Diabetes Programs Branch
Division of Diabetes, Endocrinology and Metabolic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases, NIH
Westwood Building, Room 626
Bethesda, MD 20892
Telephone: (301) 496-7888

OR

Dr. Joan T. Harmon
Executive Director, Diabetes Research Program
Diabetes Program Branch
Division of Diabetes, Endocrinology and Metabolic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases, NIH
Westwood Building, Room 622
Bethesda, MD 20892
Telephone: (301) 496-7731

ONGOING PROGRAM ANNOUNCEMENTS

RAPID ASSESSMENT POST-IMPACT OF DISASTER

PA: PA-91-04

P.T. 34; K.W. 0715095, 0730050

National Institute of Mental Health

The National Institute of Mental Health is issuing a new announcement, the Rapid Assessment Post-Impact of Disaster (RAPID), whose purpose is to provide a mechanism to support research requiring rapid funding to permit access to a disaster area in the immediate aftermath of the event. When an emergency event of potential significance for mental health occurs with little or no warning, prompt assessment of the situation may be crucial.

Applications may be submitted by any public or nonprofit institution such as a university, college, hospital, or community agency, units of State or local government, and authorized units of the Federal Government and to for-profit institutions and entities. Women and minorities and investigators without previous NIMH support are encouraged to apply. NIMH requires applicants to give added attention (where feasible and appropriate) to the inclusion of women and minorities in study populations. If women and minorities are not to be included, a clear rationale for their exclusion should be provided.

Applications may be submitted at any time and need not await the regular research grant submission dates. RAPID applications will be handled on an expedited external peer review and award basis to meet the goals for this program. RAPID awards are not to exceed $50,000 in direct costs. RAPID awards are nonrenewable and are not to exceed 1 year. Continued support may be requested only through a regular research applications that will be fully reviewed.

Potential applicants are strongly encouraged to contact the Program Officer before submitting a RAPID applications:

Susan D. Solomon, Ph.D.
Coordinator, Emergency/Disaster Research Program
Epidemiology and Psychopathology Research Branch
National Institute of Mental Health
5600 Fishers Lane
Rockville, MD 20857
Telephone: (301) 443-3728

STUDIES ON THE EFFECT OF CYTOKINES ON IMMUNE CELLS INVOLVED IN HYPERSENSITIVITY AND INFLAMMATION

PA: PA-91-05

P.T. 34; K.W. 0710070, 0715110, 0715026, 1002004, 0755035

National Institute of Allergy and Infectious Diseases

The Division of Allergy, Immunology, and Transplantation (DAIT) of the National Institute of Allergy and Infectious Diseases (NIAID), a component of

the National Institute of Health, invites research project grant applications (R01s) for support of basic and preclinical studies on the role of cytokines on immune cells involved in allergy and inflammation.

BACKGROUND INFORMATION

In recent years, substantial progress has been made in elucidating the mechanisms by which cytokines modulate the immune response in lymphocytes. Use of newer molecular biologic and biochemical techniques has allowed great success in identifying and defining the diverse functional properties of cytokines such as the interleukins and gamma interferon, and cellular factors such as TGF-alpha and beta, and GM-CSF. An understanding of what role cytokines play in the regulation of cells involved in hypersensitivity and inflammation, has been slower to develop. A picture rich with complexity but providing numerous potential opportunities to intervene in these disease processes has begun to emerge.

There is substantial experimental evidence which defines functional and morphological differences between tissue and circulating macrophages, mast cells, and basophils. Further, recent research has identified subsets of these cells which differ in their biological and physiological functions. Representative examples are pulmonary and peripheral blood macrophages in humans, and tissue and mucosal mast cells in rats in mice. As a group, these cells are important in the etiology and pathology of numerous acute and chronic inflammatory and allergic diseases. Recent evidence indicates that a wide variety of known cytokines are involved in the maturation, differentiation, proliferation, and growth of these cells which mediate inflammation and allergy. For instance, interleukin-4 and gamma interferon have been shown to regulate serum IgE and IgG. But by the same token cytokines are thought to account in great part for the observed cell activation that appears not to be IgE-mediated. Eosinophil proliferation is elicited by GM-CSF and eosinophil differentiating factor (IL-5). Most recently, mast cells themselves have been shown to secrete cytokines such as IL-3, IL-4, IL-5, and IL-6 upon activation by cross-linking to IgE or by treatment with calcium ionophores. This opens the possibility that mast cells may regulate themselves and/or be involved in the regulation of other cells of the immune system. Thus although progress is being made on determining the roles of known cytokines on these cells, more information is needed, such as whether other known cytokines are involved with these cells.

In addition, new groups of cytokines derived both from immune and non-immune cell sources have now been shown to affect mast cells, basophils and eosinophils. Neither the number nor the biochemical and physical properties of the newly discovered cytokines that act on these cells has been adequately defined. Further, the effects of these new cytokines on other cell lineages and their roles in instigating and perpetuating inflammatory/allergic diseases are not known. Identifying newer cytokines and determining their functions holds great potential benefit. Modification or abrogation of their effects, should be of value in controlling inflammatory disease in general. The application of modern molecular methodologies will allow the identification of new mediators that play a role in inflammatory disease. The isolation and further phenotypic characterization of subsets of the cells which participate in these diseases should be valuable prognostically, and provide selective points of attack for intervention therapy.

RESEARCH GOALS AND SCOPE

The NIAID is soliciting regular research grant applications directed toward identifying, isolating, and characterizing novel cytokines and the cells upon which they act, the subsets of mast cells, eosinophils, and macrophages which participate in or instigate acute and chronic inflammatory and/or allergic diseases. Information concerned with the action of known cytokines on these cells is also sought. Accordingly, there is interest in sponsoring research projects that deal with, but are not limited to, the following topics:

a) Determining the mechanisms of action of known cytokines on mast cells, macrophages, eosinophils, or basophils.

b) Identifying and developing means to isolate or enrich, and culture (either long- or short-term) subsets of the above cells that are involved in inflammatory and/or allergic responses and determining unique markers or biological functions which define their clonotypic and phenotypic properties.

c) Determining what additional cytokines are secreted by mast cells, basophils, and eosinophils and how this secretion may regulate the function of these cells and other immune cells.

d) Identifying, isolating, and characterizing new cytokines that are secreted by or have influence on eosinophils, mast cells, and basophils.

e) Cloning the genes that encode such new cytokines and determining how they are regulated at various stages during the inflammatory and allergic processes.

In these proposals the use of newer techniques of molecular and cellular biology and protein biochemistry is strongly encouraged.

MECHANISMS OF SUPPORT

The mechanism of support will be the individual research project grant (R01). Policies that govern research grant programs of the National Institutes of Health will prevail.

APPLICATION AND REVIEW PROCEDURES

Applicants should use the standard research grant application form PHS 398 (Rev. 10/88). For purposes of identification and processing, check yes on item 2 of the face page and enter the title: "STUDIES ON CYTOKINES INVOLVED IN HYPERSENSITIVITY AND INFLAMMATION, PA-91-05". Applications will be accepted in accordance with the standard submission dates for new applications: February 1, June 1, and October 1. All applications will be assigned by the Division of Research Grants for review on the basis of established Public Health Service referral guidelines. Applications will be reviewed for scientific and technical merit by a study section in the Division of Research Grants. Following study section review, applications will receive a second-level review by the appropriate national advisory council. Applications recommended for approval will compete for available funds with all other approved applications.

Applicants should include, where feasible and appropriate, minorities and women as well as men in study populations for all clinical research efforts and to analyze, where appropriate, differences between these populations. If women and minorities are not to be included, a clear rationale for their exclusion should be provided.

The original and six copies of the application should be submitted to:

Division of Research Grants
National Institutes of Health
Westwood Building, Room 240
Bethesda, MD 20892**

Requests for additional information or questions regarding this program may be directed to Dr. Prograis.

Lawrence J. Prograis, Jr., M.D.
Chief, Asthma and Allergy Branch
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
Westwood Building, Room 752
Bethesda, MD 20892
Telephone: (301) 496-8973
FAX: (301) 402-0175

This program is described in the Catalog of Federal Domestic Assistance No. 93.855. Grants will be awarded under the authority of the Public Health Service Act, Title III, Section 301 (Public Law 78-410, as amended; 42 USC 241) and administered under PHS grant policies and Federal Regulations at 42 CFR Part 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.

SMALL GRANTS PROGRAM FOR BIOETHICS AND CLINICAL DECISION MAKING RESEARCH

PA: PA-91-06

P.T. 34; K.W. 0785130, 0783010

National Center for Nursing Research

BACKGROUND AND GOALS

The mission of the National Center for Nursing Research (NCNR) is to conduct, support, and disseminate information respecting basic and clinical nursing

research, research training, and other programs in patient care research. The National Advisory Council for Nursing Research recognizes the importance of research in the area of bioethics in clinical practice and has developed a statement of research in this area that is available from NCNR at the address below.

NCNR also sponsored an interdisciplinary bioethics workshop as a means of exploring the research opportunities in bioethics and clinical practice. Proceedings from the workshop are available from NCNR staff. As a result of both endeavors, NCNR is reissuing this program announcement to encourage qualified researchers and multidisciplinary research teams to submit applications for small-scale studies and pilot projects that focus on the bioethical issues and dilemmas central to clinical decision making that relate to clinical practice. Submitted studies must be empirically based, include an interdisciplinary perspective, and examine questions in the clinical settings where the problem exists. Moreover, it is the National Institutes of Health policy that, if women or minorities are not included in a given study, a clear rationale for this exclusion must be provided. It is anticipated that findings from pilot projects, feasibility studies, or small scale studies will provide a basis from which investigators can build larger studies.

MECHANISM OF SUPPORT

As a means of laying the groundwork for bioethics and clinical decision making research, NCNR announces the Small Grants (R03) Program for Bioethics. The R03 is a nonrenewable award limited to a total of $35,000 in direct costs for the entire project period. The project period may be up to two years. The purpose of the R03 is to provide research support for empirically-based small-scale studies, pilot projects, or feasibility studies in the area of bioethics and clinical decision making research. However, applicants may utilize alternative existing mechanisms such as the R01 or R29 for other bioethical and clinical practice studies.

ELIGIBILITY

Application to the Small Grants Program (R03) is open to both new and experienced investigators engaged in clinical research from nonprofit organizations and institutions, state and local governments and their agencies, and profit-making organizations. Submission of an R03 application precludes concurrent submission of another research grant application containing the same research proposal during that particular review cycle.

APPLICATION AND REVIEW PROCEDURES

Applications for the Small Grants Program (R03) should be submitted to the Division of Research Grants on Application Form PHS 398 (Rev. 10/88) for an annual August 23 receipt date. The mailing address is as follows:

Division of Research Grants, NIH
Westwood Building, Room 240
Bethesda, Maryland 20892**

Read GENERAL INFORMATION of the PHS 398, follow the GENERAL INSTRUCTIONS on pages 1-11 of the application kit, and use SPECIFIC INSTRUCTIONS on pages 12-22, except as indicated below. The application should be written as succinctly as possible. Appendices should not be submitted.

Page 12 - Item 2 - Check "Yes" and enter Bioethics and Clinical Decision Making, PA-91-06.

Page 14 - Item 6 - The proposed project period may be up to, but must not exceed, two years.

Page 14 - Item 8a - The amount for the total project period is $35,000 in direct costs.

Page 19 - Biographical Sketch - Do not exceed one page per biographical sketch.

Pages 20 through 22 - Follow general instructions.

Page 23 - Appendix - Do not submit an appendix.

REVIEW PROCEDURE AND CRITERIA

Applications submitted in response to this announcement will be reviewed in competition by an appropriate initial review group in NCNR in accord with the usual NIH peer review procedures and criteria. Applications will be evaluated

with respect to the following criteria: the significance and scientific merit of the proposed project; level of innovation; the probability that the study will provide a basis for more extended research in the scientific area; the investigator's background and training for carrying out the project; and the adequacy and availability of resources and facilities to carry out the project.

REPORTING REQUIREMENTS

When an award is made in response to a Small Grant (R03) application, an annual progress report and Financial Status Report must be submitted. Within 90 days after the termination of the award, a Final Progress Report is required. This final reporting requirement is the same as that for other types of research grants and is in accord with 42 CFR Part 52 and 45 CFR Part 74.

CONSULTATION WITH PROGRAM STAFF

Before preparing the R03 in bioethics and clinical decision making research, applicants should consult with the NCNR program staff about their proposed project under this announcement. Applicants should contact:

Dr. Patricia Moritz
Chief, Nursing Systems Branch
National Center for Nursing Research
Building 31, Room 5B09
Bethesda, MD 20892
Telephone: (301) 496-0523

This program is described in the Catalog of Federal Domestic Assistance No. 93.361, Nursing Research. Awards are made under the authority of the PHS Act, Sections 301, 483, 484, and 485, as amended by Public Law 99-158 and 97-219. Awards are administered under PHS grant policies and Federal regulations 42 CFR Part 52 and 45 Part 74.

MECHANISMS OF UNCONTROLLED ETHANOL INTAKE

PA: PA-91-07

P.T. 34; K.W. 0404003, 0404001, 0404000, 0710085, 1002030

National Institute on Alcohol Abuse and Alcoholism

PURPOSE

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is seeking applications using single or multidisciplinary approaches to study the mechanisms underlying uncontrolled intake of ethanol. Of particular interest is the development of behavioral models that will allow investigations of the mechanisms of ethanol craving and reinforcement. These models should be able to integrate neuropharmacological, neurochemical, neurophysiological, and neuroanatomical measures with genetic and environmental factors that may contribute to ethanol self-administration.

BACKGROUND

Nearly two-thirds of the adult population in the United States consumes alcoholic beverages. Most of these consumers have no problems with their drinking. However, 10 percent are problem drinkers and some are classified as alcoholics.

People drink ethanol presumably because of its reinforcing properties -- properties that increase the desire to drink more and more ethanol. Progress in understanding the brain mechanisms that mediate the reinforcement of behavior in relation to ethanol drinking has come from the development of animal models of ethanol self-administration that may be analogous to the human condition. Such models include those in which animals will work for ethanol and those where animals are selectively bred for ethanol preference. More research is needed to validate these models of drug-seeking behavior.

Neurochemical studies have begun to identify specific neural pathways, as well as alterations in neurotransmitter systems within particular brain structures that could account for excessive ethanol intake. Although no clear consensus exists on the exact mechanism, most researchers agree that the "brain reward system" is somehow involved in ethanol reinforcement, and that multiple structures play a role. Recent neurochemical and autoradiographic data have

linked high ethanol-seeking behavior to several neurotransmitters including dopamine, serotonin, gamma-aminobutyric acid, opiates, and glutamate.

More integrative research is encouraged on the complex interrelationships among neurobiological, genetic, environmental, and behavioral factors underlying ethanol reinforcement to elucidate how the rewarding properties of ethanol may contribute to excessive intake and the development of dependence, particularly in humans.

RESEARCH AREAS OF INTEREST

Examples of important research related to this announcement include, but are not limited to, the following:

1 Behavioral Models

Good behavioral models are needed for studying ethanol-seeking behavior. Some existing models are based on consummatory behavior, operant responding (progressive ratios, or preference ratios for multiple reinforcers), brain stimulation reward, and taste and place preference conditioning. Models are encouraged that are best suited to answer specific questions relevant to ethanol-seeking behavior. Issues such as taste aversion, nutritional and motivational factors, and psychomotor function should be taken into consideration in designing behavioral models.

Research addressing the following related questions is also encouraged: What brain areas are sensitive to brain stimulation reward following ethanol administration? What is the role of anxiety in ethanol self-administration? How can behavioral paradigms be used to elucidate the pharmacology and neurobiology of ethanol self-administration? Can a model be developed to study the transition to uncontrolled drinking? Does uncontrolled drinking play a role in the development of tolerance and dependence?

2 Behavioral Genetics of Alcohol-seeking Behavior

Research is encouraged to explore the possible genetic relationships underlying the brain reward system and its relation to ethanol-seeking behavior.

The following are some important questions to be addressed: Are strain or individual differences in high ethanol-seeking behavior (e.g., preference, operant responding), genetically correlated with other ethanol-related behaviors (i.e., seizure proneness, locomotor activity, neurosensitivity, hypothermia)? Does high ethanol consumption correlate with high consumption of other drugs of abuse? What are the neurochemical and neuroanatomical substrates of high ethanol consumption?

3 Alcohol Reinforcement and Brain Systems

Experimental designs with multidisciplinary approaches are encouraged to determine whether the mesocorticolimbic-accumbens-extrapyramidal pathway and/or other neural pathways are brain reward systems that underlie alcohol reinforcement, and whether these systems are specific for alcohol or are common brain reward systems for other drugs of abuse.

The following research areas are also of interest: How agonists, antagonists, and inverse agonists of the various neurotransmitters interact to alter ethanol self-administration. Whether neurotransmitter systems are acting in parallel or sequentially to control ethanol intake. Distinguishing between the primary and secondary neurotransmitters for ethanol effects in a multiple systems framework (e.g., whether serotonin effects are blocked by drugs acting on the dopaminergic system). How the brain reinforcement system is related to the development of physical dependence.

4 Environmental Factors

It is important to study how environmental factors interact with neurobiological factors in ethanol reinforcement, craving, and relapse. In particular, research is desirable to investigate how early environmental history, current environment, i.e., aversive vs. nonaversive, and conditioned stimuli, secondary reinforcers, route of administration, contingent vs. noncontingent administration, and physiological state, are related to high ethanol-seeking behavior in both animals and humans.

Other topics of interest include: How the methods of initiation of ethanol consumption, including rate of acquisition and asymptote achieved, contribute to high ethanol intake. The role of prior drug history, including dose and

exposure to other drugs of abuse. The role of environmental factors in relapse.

5 Neurobiological Mechanisms

For each established behavioral model, it is crucial that causality be established between changes at the molecular or cellular level and high ethanol-seeking behavior. Research is encouraged to explore methods for producing a neurochemical change at a cellular or molecular level that can initiate ethanol-seeking behavior. Multidisciplinary approaches are highly encouraged, including neurobehavioral genetics, molecular biology, neurochemistry, neurophysiology, neuroanatomy, neuropharmacology, and neuroimmunology. The use of the latest neurobiological techniques and models are desirable, including transgenic mice, immunological techniques, in vivo brain dialysis, voltammetry, brain imaging techniques, and quantitative autoradiography.

6 Therapeutic Prototypes

The ultimate goal of these research initiatives is to enhance the treatment of alcohol abuse and alcoholism. Possible treatments can include the use of pharmacological agents or behavioral conditioning. New and novel approaches to treatment of excessive or uncontrolled ethanol intake are encouraged. Those approaches that might include a small-scale clinical trial and are prototypic in nature are relevant to this announcement. Large-scale human drug trials and other related clinical research are covered under other announcements.

SPECIAL INSTRUCTIONS TO APPLICANTS REGARDING IMPLEMENTATION OF ADAMHA POLICIES CONCERNING INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH STUDY POPULATIONS

Applications/proposals for ADAMHA grants and cooperative agreements are required to include both women and minorities in study populations for clinical research, unless compelling scientific or other justification for not including either women or minorities is provided. This requirement is intended to ensure that research findings will be of benefit to all persons at risk of the disease, disorder, or condition under study. For the purpose of these policies, clinical research involves human studies of etiology, treatment, diagnosis, prevention, or epidemiology of diseases, disorders or conditions, including but not limited to clinical trials; and minorities include U.S. racial/ethnic minority populations (specifically: American Indians or Alaskan Natives, Asian/Pacific Islanders, Blacks, and Hispanics).

ADAMHA recognizes that it may not be feasible or appropriate in all clinical research projects to include representation of the full array of U.S. racial/ethnic minority populations. However, applicants are urged to assess carefully the feasibility of including the broadest possible representation of minority groups.

Applications should include a description of the composition of the proposed study population by gender and racial/ethnic group, and the rationale for the numbers and kinds of people selected to participate. This information should be included in the form PHS 398 in Section 2, A-D of the Research Plan AND summarized in Section 2, E, Human Subjects.

Applications should incorporate in their study design gender and/or minority representation appropriate to the scientific objectives of the work proposed. If representation of women or minorities in sufficient numbers to permit assessment of differential effects is not feasible or is not appropriate, the reasons for this must be explained and justified. The rationale may relate to the purpose of the research, the health of the subjects, or other compelling circumstances (e.g., if in the only study population available there is a disproportionate representation in terms of age distribution, risk factors, incidence/prevalence, etc., of one gender or minority/majority group).

If the required information is not contained within the application, the review will be deferred until it is complete. Peer reviewers will address specifically whether the research plan in the application conforms to these policies. If gender and/or minority representation/justification are judged to be inadequate, reviewers will consider this as a deficiency in assigning the priority score to the application.

All applications/proposals for clinical research submitted to ADAMHA are required to address these policies. ADAMHA funding components will not award grants that do not comply with these policies.

ELIGIBILITY

Applications for alcohol research grants may be made by public or private nonprofit or for-profit organizations, such as universities, colleges, hospitals, laboratories, units of State or local governments, and eligible agencies of the Federal Government. Women and minority investigators are encouraged to apply.

MECHANISMS OF SUPPORT

Studies conducted in response to this announcement can be performed under the R01, R03, R29, and P01 mechanisms.

APPLICATION AND REVIEW PROCEDURES

Applicants should use the grant application form PHS 398 (Rev. 10/88). The number and title of this announcement, PA 91-07 and "Mechanisms of Uncontrolled Ethanol Intake," respectively, should be typed in item number 2 on the face page of the PHS 398 application form. Page limits and limits on size of type are strictly enforced. Non-conforming applications will be returned without being reviewed.

Receipt dates for applications are February 1, June, 1, and October 1.

The signed original and six permanent, legible copies of the completed application should be sent to:

Division of Research Grants, NIH
Westwood Building, Room 240
Bethesda, MD 20892**

The Division of Research Grants, NIH, serves as a central point for receipt of applications for most discretionary PHS grant programs. Applications received under this announcement will be assigned to an Initial Review Group (IRG) in accordance with established PHS Referral Guidelines. The IRG, consisting primarily of non-Federal scientific and technical experts, will review the applications for scientific and technical merit. Notification of the review recommendations will be sent to the applicant after the initial review. Applications will receive a second-level review by an appropriate national advisory council whose review may be based on policy as well as considerations of scientific merit. Only applications recommended for approval by the Council may be considered for funding.

Applications submitted in response to this announcement are not subject to the intergovernmental review requirements of Executive Order 12372, as implemented through Department of Health and Human Services regulations at 45 CFR Part 100, and are not subject to Health Systems Agency review.

INQUIRIES

For further information, please contact:

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**THE MAILING ADDRESS GIVEN FOR SENDING APPLICATIONS TO THE DIVISION OF RESEARCH GRANTS OR CONTACTING PROGRAM STAFF IN THE WESTWOOD BUILDING IS THE CENTRAL MAILING ADDRESS FOR THE NATIONAL INSTITUTES OF HEALTH. APPLICANTS WHO USE EXPRESS MAIL OR A COURIER SERVICE ARE ADVISED TO FOLLOW THE CARRIER'S REQUIREMENTS FOR SHOWING A STREET ADDRESS. THE ADDRESS FOR THE WESTWOOD BUILDING IS:

5333 Westbard Avenue
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