NIH GUIDE

For Grants and Contracts

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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. 16, NO. 17 - May 22, 1987

NOTICES

DATED ANNOUNCEMENTS (RFPs and RFAs AVAILABLE)

ONGOING PROGRAM ANNOUNCEMENTS (PAs)

NOTICES

HERPESVIRUS SIMIAE ALERT

P.T. 16, 34; K.W. 0715125, 0785165

Division of Research Resources

NIH has learned that two confirmed clinical cases of Herpesvirus simiae (B-virus) encephalitis, a generally fatal disease in humans, have occurred among caretakers working with rhesus monkeys at a U.S. research institution. The disease reportedly was acquired through contact with a colony-born rhesus monkey that was under treatment for bilateral conjunctivitis. The Centers for Disease Control (CDC) presently is investigating the cases and will issue a summary report that will appear in "Morbidity and Mortality Weekly Report" when the investigation is complete. In the meantime, CDC recommends that the precautions recommended on page 63 in the CDC NIH Publication (HHS Publication No. (CDC) 84-8395) "Biosafety in Microbiological and Biomedical Laboratories" continue to be observed by personnel working with nonhuman primates, especially macaques and other Old World species where exposure to Herpesvirus simiae is a possibility.

DIRECT SUBMISSION OF NUCLEIC ACID AND PROTEIN DATA TO GENBANK, PROTEIN IDENTIFICATION RESOURCE, AND PROTEIN DATA BANK

P.T. 36; K.W. 0755045, 0760070

National Institute of General Medical Sciences

The biological databases providing nucleic acid and protein data are expected to grow rapidly in the next few years. Those supported by NIH in collaboration with NSF, DOE, and USDA are: GenBank--the nucleic acid sequence database; Protein Identification Resource--the protein sequence database; and the Protein Data Bank--a repository of crystallographic coordinates and structure factors of macromolecules. In order that these databases remain current with the information appearing in the literature, it has become necessary to ask authors to submit their sequence or structure data directly to the appropriate database as soon as the data have been accepted for publication by a journal. Authors who do so will, in addition to ensuring that the database is kept up-to-date, be pleased to see that their data will appear in the database soon after submission.

To facilitate the submission of data, the investigator is encouraged to contact the appropriate database for information as indicated below:

GENBANK:

GenBank will provide data request forms. To obtain forms, authors may call GenBank at (505) 667-7510. They may also contact GenBank on BITNET/ARPANET at GENBANK@LANL.GOV or GENBANK on the Bionet mail system.

Those interested in obtaining copies of the database or who need general information should contact Bolt, Beranek and Newman at (617) 497-2742.

PROTEIN IDENTIFICATION RESOURCE (PIR):

Protein sequence data can be submitted as clean copy or on a magnetic tape. Investigators who are unfamiliar with the PIR format or would like additional information should contact the the PIR data acquisition manager at (202) 625-2121. The database may also be contacted on Bitnet at PIRMAIL@GUMBRF.

PROTEIN DATA BANK:

The Protein Data Bank accepts data from investigators in machine readable form (e.g., magnetic tape). A data deposition form can be obtained by calling the Brookhaven National Laboratory at (516) 252-4382.

NIH/FDA REGIONAL WORKSHOP - PROTECTION OF HUMAN SUBJECTS

P.T. 42; K.W. 0783005

National Institutes of Health
Food and Drug Administration

The National Institutes of Health (NIH) and the Food and Drug Administration (FDA) are continuing to sponsor a series of workshops on responsibilities of researchers, Institutional Review Boards (IRBs), and institution officials for the protection of human subjects in biomedical and behavioral research. The workshops are open to everyone with an interest in research. The meetings should be of special interest to those persons currently serving or about to begin serving as a member of an IRB. The current schedule includes:

Date: October 1-2, 1987

Location: San Antonio, TX

Contact:

Sue Hoppe, Ph.D.
University of Texas
Health Science Center
7703 Floyd Curl Drive
San Antonio, TX 78284
Telephone: (512) 567-2350

Additional workshops will be announced later. For further information regarding education programs contact:

Darlene M. Ross
Education Program Coordinator
Office for Protection from Research Risks
National Institutes of Health
Building 31, Room 4B09
Bethesda, Maryland 20892
Telephone: (301) 496-8101

DATED ANNOUNCEMENTS (RFPs and RFAs AVAILABLE)

DEVELOPMENT AND IMPLEMENTATION OF MECHANISTICALLY-ORIENTED ANTI-HIV DRUG PRESCREENS--SOURCES SOUGHT

ANNOUNCEMENT NO. NCI-CM-87234-29

P.T. 34; K.W. 0740020, 1002045, 0755010

National Cancer Institute

The National Cancer Institute is planning to award multiple contracts for development and implementation of mechanistically-oriented anti-HIV drug prescreens. These contracts will address various aspects of the viral life-cycle which may be exploited as therapeutic targets. Infection of susceptible human cells by human immunodeficiency virus (HIV), the etiologic agent of acquired deficiency syndrome (AIDS), has been shown to involve a series of steps common to other retroviral infections, i.e. binding of viral particles to cellular receptors, internalization of the virus, transcription of viral RNA into DNA via the viral enzyme reverse transcriptase, integration of the viral DNA transcript into host chromosomal DNA, and subsequent transcription of viral DNA resulting in the synthesis and release of new infective virions. These steps offer multiple possibilities for the development of new agents useful for therapeutic purposes. To date, efforts have centered on development of drugs which inhibit the viral reverse transcriptase enzyme and/or which can be shown to directly inhibit viral cytopathic effects in vitro. Other biochemical/molecular systems besides reverse transcriptase have received relatively little attention and none has been the focus for a large-scale screening program.

In order to accomplish an effort of this nature, any organization responding to this announcement must have the capability to develop and evaluate drug screening assays which address biochemical/molecular targets relevant to identification of compounds with potential anti-HIV activity. Work should be directed towards development of

screening assay methodology which can be implemented on a scale suitable for testing at least 10,000 unknown materials annually. Following the demonstrated feasibility of proposed assay methods, the organization must be capable of implementing a large-scale mechanistically-oriented prescreen capable of testing at least 10,000 unknown materials annually. Firms, individuals, or organizations should indicate their interest in developing and implementing a mechanistically-oriented prescreen by responding no later than May 29, 1987.

Respondents should briefly describe proposed assay methods and broad capabilities in a non-proprietary fashion and indicate their experience and expertise in these areas. This announcement is to solicit expressions of interest and information for purposes of program planning. It does not constitute an RFP and is not to be construed as a commitment by the Government. Responses will be used to establish a source list for solicitation.

All respondents will receive copies of any solicitations resulting from this announcement. Submit written responses to the attention of:

Clyde Williams
Contracting Officer
Treatment Contract Section
Research Contracts Branch, NCI
Blair Building, Room 224
Bethesda, Maryland 20892
Telephone: (301) 427-8737

PRIMARY PREVENTION TRIAL OF BARRIER CONTRACEPTIVES AGAINST HTLV-III INFECTION - SUBCONTRACTING SOURCES SOUGHT

P.T. 34; K.W. 0715125, 0750020, 0755015

National Institute of Child Health and Human Development

The University of California, Los Angeles (UCLA), under prime contract No, N01-HD-6-2934 with the National Institute of Child Health and Human Development, NIH, is seeking sources worldwide, to participate in a pilot randomized clinical trial of barrier contraceptives against Human Immunodeficiency Virus (HIV) infection.

The objectives of the trial will be to demonstrate: 1) The successful deployment, acceptance and use of a maximum barrier regimen, consisting of condoms plus spermicide, in a high risk heterosexual population; 2) the medical safety of the spermicidal agent; and, if possible, 3) the efficacy of the maximum barrier regimen measured by the relative risk of seroconversion in maximum barrier users compared to non-users or users of other products.

The offeror must be capable of providing a stable, high risk heterosexual target population, consisting of high risk men, women or couples with some history of current or past contraceptive use or the likely prospect of future use of barrier contraceptives. A high risk population shall have a 10-50 percent prevalence of HIV infected persons or an annual incidence of HIV infection greater than 5 percent per year. A stable population shall be non-mobile; i.e. available for 3-month periodic follow-ups over 12-24 months. The proposed study population must consist of at least 200-400 non-users of intravenous drugs per risk group, depending on the projected incidence of the disease, and shall be located in a city or an area which has reliable and rapid communications via telephone and airlines with Los Angeles, California. Administration of the pilot study will require the following: 1) a competent and willing local investigator, thoroughly familiar with the culture of the country in which the target population resides; 2) availability of a competent staff to provide health screening, interview and follow-up, and collection of specimens; 3) a laboratory which can separate cells from serum and plasma, aliquot specimens for storage, and freeze specimens at -20 C for rapid transport to Los Angeles, California.

All respondents should provide descriptions of: 1) Background and research interests and experience of the local investigator(s); 2) Backgrounds of potential staff members, by name, training, or experience histories, 3) Laboratory capabilities. Where applicable, the statement of capabilities should include mention of on-site or local facilities capable of further processing specimens for ELISA testing of HIV antibody, Western blot testing, counts of CD-4 and CD-8 T-cell subsets, and serologic and isolation studies of CMV, EBV, HSV-2, and Hepatitis-B; 4) Local or regional availability of contraceptive products, family planning services, or other evidence that study populations will be willing to use barrier contraceptives for themselves and their partners given proper documents; 5) Local, regional, or national interest in AIDS study, prevention, or treatment.

This announcement is not a request for proposals (RFP) and responses should not contain pricing or budgetary information. Organizations that believe they can meet the requirements of this project should submit five (5) copies of their capability statement, citing Synopsis No. NICHD-87-04, to each of the following addresses by C.O.B. June 8, 1987:

Paul J. Duska, Contracting Officer
Contracts Management Section, OGC
National Institute of Child Health and Human Development
Landow Building, Room 6C25
7910 Woodmont Avenue
Bethesda, Maryland 20892

Dr. Roger Detels, ABC Study Principal Investigator
UCLA School of Public Health
Center for Health Sciences, 73-265
Los Angeles, California 90024

SYNTHESIS OF CONGENERS AND PRODRUGS OF ANTI-AIDS COMPOUNDS

RFP AVAILABLE: NCI-CM-87216-16

P.T. 34; K.W. 0740020, 0755025, 1003012

National Cancer Institute

The Drug Synthesis And Chemistry Branch (DS&CB), of the Developmental Therapeutics Program (DTP), of the Division of Cancer Treatment (DCT), of the National Cancer Institute (NCI), National Institutes of Health (NIH), has a requirement for contractors with chemical synthesis and drug design expertise to synthesize a variety of compounds for evaluation as potential anti-AIDS agents.

The assigned objectives of this project will be: (a) to design and synthesize congeners and prodrugs and other compounds with confirmed activity; (b) to design and synthesize prodrugs and other compounds that possess elements of both congener and prodrug; (c) to synthesize compounds related to products of natural origin and other related heterocycles; and (d) to synthesize anti-sense nucleic acids.

Each contractor should have available a fully operational facility, including all necessary equipment and instrumentation for all aspects of the contract.

The nature of this project requires that the following restrictions be applied:

The NCI signs legally binding agreements with certain suppliers (often pharmaceutical or chemical companies) which state that all information on compounds submitted by the supplier will be held confidential. The successful offeror will be expected to synthetically modify such commercially confidential (discreet) materials. Thus, pharmaceutical or chemical companies could obtain valuable data on new lead compounds. Therefore, in order to honor the confidentiality agreement with the supplier, the NCI believes that the compounds cannot be sent to potential competitors of the supplier and, thus, pharmaceutical and chemical companies must be excluded from the competition.

Request for Proposal (RFP) NO. NCI-CM-87216-16 will be issued on or about June 3, 1987, and proposals will be due approximately six weeks thereafter(on or about July 20, 1987.). To expedite requests for solicitation, please furnish three self-addressed labels with your request. The contract period is to be three years, beginning approximately April 1, 1988, at a level of effort of approximately 6,650 hours/year/contract period. Three cost-reimbursement contracts are expected to be awarded.

Copies of the RFP NO. NCI-CM-87216-16 may be obtained by sending a written request to:

Patricia L. Shifflett
Contract Specialist
Treatment Contracts Section, Research Contracts Branch
National Cancer Institute
Blair Building, Room 216
Bethesda, Maryland 20892

CORONARY HEART DISEASE AND STROKE IN PEOPLE AGED 65 TO 84 YEARS--CENTRAL BLOOD ANALYSIS LABORATORY

RFP AVAILABLE: NIH-NHLBI-HC-87-05

P.T. 34; K.W. 0750010, 0715040, 0715200

National Heart, Lung, and Blood Institute

The Epidemiology and Biometry Research Program, DECA, NHLBI, seeks a Central Blood Analysis Laboratory for a project in which four field centers will recruit, examine, and follow a total of 5000 men and women (1250 in each center) aged 65 to 84 years at the baseline examination in a prospective study of coronary heart diseases and stroke. The Central Blood Analysis Laboratory will develop a protocol for collection of blood samples at the four field centers; will perform precise measures of lipids and apolipoproteins (apo's for case-control study only), hemostasis factors, insulin, glucose; and will provide quality control of blood collection at the field centers and of measurements in the blood laboratory itself.

In addition to this RFP for the Central Blood Analysis Laboratory, a separate RFP will be announced when it becomes available for the Ultrasound Reading Center. RFPs for the Field Centers, Coordinating Center, and Echocardiography Reading Center have already been announced.

RFP NHLBI-HC-87-05 for the Central Blood Analysis Laboratory will be available on or about July 6, 1987, with proposals due approximately September 4, 1987. One award is anticipated. Your written request should include three mailing labels, self-addressed, and must cite RFP No. NHLBI-HC-87-05.

Requests for copies of the RFP should be sent to:

Betty Nordan
Contracting Officer for Epidemiology and
Biometry Research Program,
ECA Contracts Section
National Heart, Lung, and Blood Institute
Federal Bldg., Room 3C16
Bethesda, Maryland 20892

SEXUALLY TRANSMITTED DISEASES RESEARCH UNITS

RFA AVAILABLE: 87-AI-20

P.T. 34; K.W. 0715220, 0785055, 1002027, 0745020, 0745055, 0415000

National Institute of Allergy and Infectious Diseases

Application Receipt Date: November 16, 1987

BACKGROUND INFORMATION

The National Institute of Allergy and Infectious Diseases (NIAID) invites applications for program project grants to be initiated during FY1988 for a continuing program of research on Sexually Transmitted Diseases (STD) but excluding acquired immunodeficiency disease syndrome (AIDS).

RESEARCH GOALS AND SCOPE

The goal of the program is to encourage investigators to undertake research that will provide the clinical, epidemiological and microbiological information needed for the eventual control of sexually transmitted diseases. The NIAID wishes to broaden the scope of its program of research in this area so that the knowledge gained may be applied to improvement in the means of prevention, diagnosis, and therapy of these infections.

As one means of achieving the stated goals, the NIAID proposes to maintain support of a number of STD Research Units. These units are funded as program project grants, function as centers of excellence in STD research and serve as foci for research and training. The research to be considered for emphasis in this program can be on any or on all of the STDs that are currently recognized as significant public health problems with the exceptions of AIDS and ectoparasites. A strong clinical component should be a major part of the program project application. Several

distinguishing characteristics that must be considered in developing these applications for STD Research Units and the specific areas of research being encouraged are detailed in the full RFA.

Only institutions with demonstrated expertise in both clinical and basic sciences and with strong ongoing research programs and resources that can focus on a multidisciplinary and multifaceted team effort to study in depth STD infections will be considered for program project support under the provisions of this program.

MECHANISM OF SUPPORT

Eligibility: Domestic universities, medical colleges, hospitals, laboratories and other public or private research institutions, including State and local governmental units, are eligible.

Length of Support: The project can be supported up to a maximum of five years without additional competition contingent upon availability of funds.

Expected Number of Awards: Competition is open for three (3) program projects in STD research. Three currently funded STD Research Units will be competing for renewal of their support. Support for each STD Research Unit is estimated at $350,000 to $450,000 per year, direct costs.

APPLICATION PROCEDURES

All applications in response to this RFA must be submitted on Application Form 398. The RFA label available from the NIAID contact person listed below must be affixed to the bottom of the face page. Failure to use this label could result in delayed processing of your application such that it may not reach the review committee in time for review.

All inquiries and requests for the full text of this RFA should be directed to:

William P. Allen, Ph.D., Chief
Bacteriology and Virology Branch, MIDP
National Institute of Allergy and Infectious Diseases
Westwood Building, Room 738
Bethesda, Maryland 20892
Telephone: (301) 496-7728

It is strongly suggested that interested investigators submit a letter of intent by September 30, 1987 to the Institute contact person. This letter should include a descriptive title of the proposed program project and indivudual subprojects and the names of the proposed program director and subproject investigators. The letter is not mandatory and is not binding; it will not enter into the review of any application subsequently submitted.

MECHANISMS OF ACTION OF THE DRUG CYCLOSPORINE

RFA AVAILABLE: 87-AI-19

P.T. 34; K.W. 0740025, 0710070, 0745040, 0745065, 0760075, 0710100

National Institute of Allergy and Infectious Diseases

Application Receipt Date: September 15, 1987

BACKGROUND INFORMATION

Cyclosporine A (CsA) has been used for several years to suppress allograft rejection in patients receiving organ transplants. The use of cyclosporine is reported to be of major importance in improving the survival of kidney, liver, heart, bone marrow and pancreas transplants. This agent appears to have selective rather that broad spectrum activity. However, the exact mechanism of its action is unknown. Helper T lymphocytes appear to be the main target of CsA action. Controversial claims suggest that CsA affects T or B lymphocytes or both, and that it affects the balance of immunoregulatory cells.

Despite the growing importance of CsA in organ transplantation, toxicity episodes, especially to the kidney, continue to be a major limitation. Long term effects of cyclosporine treatment have not been fully elucidated with respect to increased susceptibility to infection or increased development of malignancies.

RESEARCH GOALS AND SCOPE

The National Institute of Allergy and Infectious Diseases (NIAID) is soliciting investigator-initiated research grant applications that are designed to increase knowledge and understanding of the mechanism of cyclosporine's immunosuppressive action and elucidate its side effects.

1 The nature of cellular receptor sites, cell specificity T and B lymphocyte interactions and subcellular mechanisms that might be involved in the mode of action of the drug.
2 The influence of genetic differences on CsA action.
3 Immunosuppressive properties of CsA.
4 Pathogenetic and biochemical mechanisms of nephrotoxocity.
5 Development of a drug that can modify or eliminate toxicity of CsA.
6 Pharmacodynamic interactions between CsA and other agents.
7 Studies on long term effects of cyclosporine.

MECHANISMS OF SUPPORT

The mechanism of support will be the traditional research project grant. Policies that govern research grant programs of the National Institutes of Health will prevail. The award of grants pursuant to this RFA is contingent upon receipt of proposals of high scientific merit and the availability of appropriated funds. In fiscal year 1988, the NIAID plans to fund at least two new awards in response to this RFA.

METHOD OF APPLYING

Use the standard research grant application form PHS 398. For purposes of identification and processing, the words "MECHANISMS OF ACTION OF THE DRUG CYCLOSPORINE" should be typed in item 2 on the face page of the application and a brief covering letter should be attached indicating submission is in response to the NIAID accouncement. The original and five copies of the application should be submitted to:

Application Receipt Office
Division of Research Grants
National Institutes of Health
Westwood Building, Room 240
Bethesda, Maryland 20892**

The RfA label obtained from the NIH staff person named below must be affixed to the bottom of the face page. Failure to use this label could result in delayed processing of your application such that it may not reach the review committee in time for review.

STAFF CONTACT

A more detailed RFA may be obtained from:

Dr. Jane S. Schultz
Chief, Genetics and Transplantation
Biology Branch, IAIDP
National Institute of Allergy
and Infectious Diseases
Westwood Building, Room 754
Bethesda, Maryland 20892
Telephone: (301) 496-5598

SURGICAL ONCOLOGY RESEARCH TRAINING GRANTS (T32)

P.T. 44; K.W. 0785140, 0785210

National Cancer Institute

Application Receipt Date: September 10, 1987

Surgical Oncology Research Training grant applications (T32) are invited by the National Cancer Institute. There is but one receipt date per year, namely September 10. Applications received by September 10, 1987 will be reviewed for scientific merit by an ad hoc review group based in the National Cancer Institute's Division of Extramural Activities and by the National Cancer Advisory Board. These reviews will be completed in time to permit funding by July 1, 1988. Interested parties should contact the person indicated below for a copy of the guidelines.

Program Director
Surgical Oncology Research Training
Cancer Training Branch, CCSP,
Division of Cancer Prevention
and Control
National Cancer Institute, NIH
Blair Building, Room 428
9000 Rockville Pike
Bethesda, Maryland 20892-4200
Telephone: (301) 427-8866, 427-8855 or 427-8898

ONGOING PROGRAM ANNOUNCEMENTS (PAs)

CANCER EDUCATION GRANTS (R25) (PA)

P.T. 34; K.W. 0502000, 0502028, 0745055

National Cancer Institute

The National Cancer Institute announces the resumption of competition for Cancer Education Grants (R25), but under new guidelines. Any institution wishing to compete should request a copy of the guidelines from the office listed below.

The new grant has three major aspects, namely:

1 Multiyear training in the interventive practice of chronic disease prevention and control (with a focus on cancer), such training to lead to a degree such as the Doctor of Public Health;

2 Support for up to five years for the development of nutrition curricula for the aforementioned schools, again with an emphasis upon the prevention and control of chronic diseases, especially cancer; and

3 Summer research experience support for students in schools of medicine, dentistry, nursing, public health and allied health.

An applicant may seek support for one or more of these three projects. The receipt dates for applications shall be October 1, February 1, and June 1 each year until further notice. Applications received by October 1, 1987 shall be fundable on or about July 1, 1988. In that fiscal year (1988) it is anticipated that the program will have sufficient funds to support summer student activities at a reduced level; support up to three or four new training projects in disease prevention and control; and support up to seven nutrition curriculum projects. At this time it is impossible to estimate the amount of money which will be available for new starts in FY 1989.

Please address inquiries to:

Program Director
Cancer Training Branch, CCSP,
Division of Cancer Prevention
and Control
National Cancer Institute, NIH
Blair Building, Room 428
Bethesda, Maryland 20892-4200
Telephone: (301) 427-8866 or 427-8855

This program is described in the Catalog of Federal Domestic Assistance No. 13.398, Cancer Research Manpower. Awards will be made under the authority of the Public Health Service Act, Section 301 (42 USC 241) and Section 403 (42 USC 284) and administered under PHS Grant Policies and Federal Regulations, most specifically at 42 CFR Part 52 and 42 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or to Health Systems Agency review.

MINORITY PARTICIPATION IN BIOMEDICAL RESEARCH (PA)

P.T. 34, FF; K.W. 0715085, 0715075, 0715135

National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Diabetes and Digestive and Kidney Diseases

The Health and Human Services Secretary's Task Force on Black and Minority Health was charged with investigating the health problems of Blacks, Native Americans, Hispanics and Asian/Pacific Islanders. In addition to specific recommendations in a variety of areas, the Task Force emphasized the need for continued research and analysis to increase the base of scientific knowledge about factors that put minorities at greater risk for illness and death.

The National Institute of Arthritis and Musculoskeltal and Skin Diseases and the National Institute of Diabetes and Digestive and Kidney Diseases recognize the continuing, significant difference between the health of racial/ethnic minorities in the United States and the general population. In order to reduce the minority health disparity, these Institutes seek to stimulate research on both acute and chronic diseases in minority populations. This Program Announcement complements other ongoing activities to increase minority participation in biomedical research supported by these Institutes.

A variety of support mechanisms are available. For further information about the appropriate mechanism, contact:

Steven J. Hausman, Ph.D.
Deputy Director, Extramural Activities Program
National Institute of Arthritis and Musculoskeletal and
Skin Diseases
Westwood Building, Room 403C
Bethesda. Maryland 20892
Telephone: (301) 496-7495

Lois F. Lipsett, Ph.D.
Chief, Special Programs Branch
Division of Diabetes, Endocrinology, and Metabolic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
Westwood Building, Room 620
Bethesda, Maryland 20892
Telephone: (301) 496-7433

Charles Rodgers, Ph.D.
Director, Urology Program
Division of Kidney, Urologic, and Hematologic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
Westwood Building, Room 609C
Bethesda, Maryland 20892
Telephone: (301) 496-7574

Ralph L. Bain, Ph.D.
Director, Digestive Diseases Centers Program
Division of Digestive Diseases and Nutrition
National Institute of Diabetes and Digestive and Kidney Diseases
Westwood Building, Room 3A15
Bethesda, Maryland 20892
Telephone: (301) 496-9717

These programs are described in the Catalog of Federal Domestic Assistance Nos. 13.846, 13.847, 13.848, and 13.849. Awards will be made under the authority of the Public Health Service Act, Section 301 (42 USC 241) and administered under PHS Grant Policies and Federal Regulations, most specifically 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 to Health Systems Agency review.

RESEARCH ON CARDIOPULMONARY DISORDER OF SLEEP (PA)

P.T. 34; K.W. 0715040, 0715165, 0710100, 0705065, 1002019, 0785055

National Heart, Lung, and Blood Institute

The Division of Lung Diseases (DLD) of the National, Heart, Lung, and Blood Institute (NHLBI) encourages the submission of research grant applications related to basic and clinical research on cardiopulmonary disorders during sleep.

BACKGROUND

Cardiopulmonary disorders during sleep and particularly the sleep apnea syndrome, are now recognized as common clinical disorders that can range in severity from mild abnormalities in blood oxygen saturation, fragmented sleep, and mild daytime drowsiness to severe hypersomnolence, extreme hypoxia, and potentially life threatening cardiopulmonary failure. The hallmark of the syndrome is excessive daytime sleepiness and diminished quality of life during daytime. The prevalence of sleep apnea syndrome in this country is largely unknown; however, data from population studies suggest a prevalence of approximately 2 to 4 percent of the general population, and a considerably higher incidence among those who are obese or hypertensive. Research on these disorders has increased steadily, and basic research is rapidly becoming relevant to clinical problems and treatment.

RESEARCH GOALS AND SCOPE

The goal of this program announcement is to stimulate a multidisciplinary approach to integrate basic sleep research, as it relates to the heart and lungs, to recognizable clinical cardiopulmonary disorders of sleep.

The research scope of this program is broad and will encompass a wide spectrum of basic and clinical research disciplines including aspects of pulmonary medicine, cardiopulmonary physiology, pharmacology, sleep physiology, biochemistry, molecular biology, genetics, and epidemiology. Thus, grant applications are invited on topics that may range from fundamental research on the pathophysiology of sleep disordered cardiopulmonary function to clinical studies on the diagnosis, treatment, management, prevention and natural history of cardiopulmonary sleep disorders, including the relationship between hypertension and overall cardiovascular dysfunction in patients with clinical cardiopulmonary sleep disorders. Some examples of relevant research areas are given below, but applications are not limited to these topics.

1 Neural control of respiration during sleep

The events that initiate, terminate and regulate the duration of an apneic event are currently unknown. It has been reported that respiratory modulated neuronal activities are depressed by quiet sleep; however, many neurons are relatively unaffected by sleep. Additional studies are needed using chronically instrumented, non-anesthetized preparations during physiologic sleep to define the role of the CNS in control of respiration during sleep. Other major questions on CNS control of breathing during sleep include the origin of the wakefulness stimulus, separation of the effects of respiratory from non-respiratory neurons, and differentiation of respiratory neural activation on chest wall versus upper airway motor neurons. What role do the CNS mechanisms which produce sleep have in the pathogenesis of cardiopulmonary disturbances during sleep?

2 Pharmacology

A number of studies are underway on the basic question of the neurochemical agents responsible for sleep. However, virtually nothing is known concerning the effects of these putative sleep modulations on respiratory neurons, nor has any attention been given to the link between sleep apnea and any of these neurochemicals. The neurochemical agents responsible for sleep may have relevance for treatment of clinical cardiopulmonary sleep disorders.

3 Respiration and Metabolism

There are a number of unresolved questions related to the regulation of the pharyngeal airway, the pharmacology of the upper airway, and the structural changes of the bony and soft tissue structures of the upper airway in obstructive sleep apnea that hold considerable promise for future research. Studies are needed to identify the primary site of obstruction and if it varies within or between subjects, and if useful information can only be obtained during sleep, or whether quantitative anatomic measures during wakefulness can be related to events in sleep. Studies are also needed to develop useful animal models for the obstructive sleep apnea syndrome. Studies investigating the mechanisms through which increased body

weight contributes to development of sleep disordered breathing, and the link between body weight, upper airway anatomy and sleep apnea need clarification. Lastly, studies of gender/sex hormone effects aimed at explaining the male predominance of sleep disordered breathing might produce information with therapeutic implications.

4 Genetics and Molecular Biology

Sleep apnea syndrome has been shown to exhibit familial clustering. Whether there is specific genetic basis for these observations is unknown. However, well documented disturbances of sleep that are clearly hereditary pave the way for molecular biologists to examine cellular receptors, specific proteins, and possible identify gene abnormalities.

5 Cardiovascular Function

A number of clinical and physiological observations have pointed to a link between respiratory disorders during sleep and systemic hypertension. It has been estimated that some 60-80 percent of patients with sleep apnea have hypertension. However, there have been no rigorous cardiovascular studies that have been undertaken to investigate this relationship. For example, what aspect of sleep disturbance produces hypertension, and does sleep fragmentation or sleep deprivation produce hypertension? It is also of interest that many cardiovascular diseases have diurnal variation. For example, strokes and myocardial infractions have been shown to occur mostly in the early morning hours. Is there any casual relationship between sleep states, respiratory, and circulatory dynamics, which act in concert to trigger these fatal events?

6 Epidemiology

Epidemiologic studies of patients who develop cardiopulmonary disorders of sleep are badly needed since the natural history of the sleep apnea syndrome is largely unknown. In addition, there is no clear distinction between pathologic and physiologic respiratory abnormalities, nor is there a clear relationship between objective measures of disordered breathing, sleep disturbance, and morbidity or mortality. Further studies are needed to explore these questions to define natural history and delineate clinical implications of sleep findings.

MECHANISM OF SUPPORT

The support mechanism for grants in this area will be the traditional investigator-initiated research grant. Applications submitted in response to this announcement will be brought to the attention of the National Heart, Lung, and Blood Advisory Council and will receive special consideration for support by the NHLBI. The Institute considers this the first phase in our long range plans to build a program in cardiopulmonary sleep research, which includes the possibility of announcing a new specialized centers of research program in cardiopulmonary disorders of sleep in the future. Institute staff would be willing to visit prospective programs to discuss development of research related to cardiopulmonary disorders of sleep. Interested persons are urged to contact program staff for information related to this announcement.

APPLICATION AND REVIEW PROCEDURES

The receipt dates for applications submitted in response to this announcement are October 1, February 1, and June 1. Applicants should use the regular research grant application Form PHS 398, which is available at most institutional business offices or the Division of Research Grants (DRG), NIH.

Applications in response to this announcement will be reviewed in accordance with the usual Public Health Service peer review procedures for research grants by the Division of Research Grants. Review criteria include the significance and originality of the research goals and approaches; feasibility of the research and adequacy of the experimental design; research competence; adequacy of available facilities; provisions for the humane care of animals and human subjects, and appropriateness of the requested budget relative to the work proposed. Funding decisions will be based on Initial Review Groups' recommendations, and special consideration by the National Heart, Lung, and Blood Advisory Council. Secondary review for applications assigned other institutes would be by the appropriate National Advisory Council.

To identify responses to this announcement check "yes" and put "Research on Cardiopulmonary Disorders of Sleep" under item 2 of page 1 of those grant applications relating to the topics identified herein.

The original and six copies of the application should be mailed to the following address:

Application Receipt Office
Division of Research Grants
National Institutes of Health
Westwood Building, Room 240
Bethesda, Maryland 20892**

The DRG will assign applications for review according to the NIH process for research grant applications.

For further information applicants may contact:

James P. Kiley, Ph.D.
Structure and Function Branch
Division of Lung Diseases
National Heart, Lung, and Blood Institute
National Institutes of Health
Westwood Building, Room 6A07
Bethesda, Maryland 20892
Telephone: (301) 496-7171

This program is described in the Catalog of Federal Domestic Assistance No 13.838, Lung Diseases Research. Awards will be made under the authority of the Public Health Service Act, Title III, Section 301 (Public Law 73-410, as amended; 43 USC 241) and administered under PHS grant policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372, or to Health Systems Agency review.

** THE MAILING ADDRESS GIVEN FOR SENDING APPLICATIONS TO THE DIVISION OF RESEARCH GRANTS 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 STREET ADDRESS FOR THE WESTWOOD BUILDING IS:

5333 Westbard Avenue
Bethesda, Maryland 20816

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