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. 1, JANUARY 9, 1987

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NATIONAL RESEARCH SERVICE AWARDS (NRSA)--INSTITUTIONAL TRAINING GRANTS

P.T. 44; K.W. 0720005, 0785130

National Center for Nursing Research (NCNR)

Initial Application Receipt Date: February 25, 1987
Subsequent Application Receipt Dates: May 10, June 10, September 10, 1987

The National Center for Nursing Research (NCNR) wishes to bring to the attention o the directors of doctoral programs in nursing that opportunities exist for institutions to apply for research training grants to support four or more predoctoral students. The inclusion of one or two postdoctoral positions is permitted. The environnment for multidisciplinary research training involving mor than one unit of a university, a recruitment plan that will attract the most highl qualified candidates from throughout the nation, and the ability to demonstrate th graduates of the program remain active in research will be of particular importanc Applicant institutions should have a strong graduate school in the biomedical and behavioral sciences.

Applications received by February 25, 1987 will have their initial review in May f consideration by the June NCNR Council with funding anticipated for a July 1, 1987 start date. This is an accelerated review schedule. In the future, although the established NIH NRSA application receipt dates (January 10, May 10, September 10) will apply, applications will be considered only by the NCNR January/February Council for grants to be awarded on the following July 1.

For application materials, contact:

Office of Grants Inquiries
Westwood Building, Room 449
National Institutes of Health
Bethesda, Maryland 20892
Telephone: (301) 496-7441

For additional information, contact:

National Center for Nursing Research
Building 38A, Room B2E17
National Institutes of Health
Bethesda, Maryland 20892
Telephone: (301) 496-0526

TARGETING DRUGS TO THE CENTRAL NERVOUS SYSTEM FOR AIDS THERAPY

RFP AVAILABLE: NIAID-AIDSP-87-16

P.T. 34; K.W. 0715120, 0740020, 0755025

National Institute of Allergy and Infectious Diseases

The Treatment Branch, AIDS Program, National Institute of Allergy and Infectious Diseases (NIAID), NIH, has a requirement for targeting drugs for AIDS therapy to t central nervous system (CNS). The modification to antiviral drugs identified as effective against HTLV-III/LAV/HIV in vitro by the screening efforts of NIAID or drug discovery groups may be required to allow the delivery of drugs to the CNS. The objective of this proposed project is to ensure that efforts will be made now develop the expertise necessary to deliver drugs to the CNS. The NIAID, in collaboration with the United States Army Research Development Command, has established a rapid, large scale, in vitro screening program to evaluate the effectiveness of potential HTLV-III/LAV/HIV drugs. NIAID will undertake the lead role this year, in collaboration with the NCI, in organizing scientists into group focused on the discovery of novel drugs for the treatment of AIDS. Through these efforts and other independent efforts, drugs which will prevent the replication of retroviruses will be identified and developed by the AIDS Program.

Drugs which prevent HTLV-III/LAV/HIV replication may cross the blood-brain barrier rapidly (Azidothymidine), slowly (Dideoxycytidine, Ribavirin), or not at all. Recent reports have shown the ability to make dihydropyridine derivatives of nucleosides by the attachment of a chemical carrier through an ester linkage. The modified drugs (termed prodrugs) are greatly enhanced in their ability to cross th blood-brain barrier. The successful development of improved methods for delivery and targeting of effective agents to the CNS will be especially beneficial to halt the progression of the disease, the spread of the infection, and control a reservo of the virus. The purpose of this solicitation is two-fold: first, to modify kno antiretroviral drugs to increase their ability to cross the blood-brain barrier; second, to encourage the development of innovative approaches for targeting drugs the central nervous system.

This announcement is a new solicitation. RFP-NIH-NIAID-AIDSP-87-16 shall be issue on or about January 5, 1987, with a closing date tentatively set for March 3, 1987

To receive a copy of the RFP please supply this office with two (2) self-addresse mailing labels.

Requests should be addressed to:

Frank M. Fountain
Contract Specialist, Contract Management Branch
NIAID, NIH
Westwood Building, Room 707
5333 Westbard Avenue
Bethesda, Maryland 20892.

All inquiries must be in writing; telephone inquiries will not be honored. All responsible sources may submit a proposal which shall be considered by the NIAID.

This advertisement does not commit the Government to award a contract.

PULMONARY COMPLICATIONS OF HTLV-III/LAV INFECTION

RFP AVAILABLE: RFP-NHLBI-HR-87-09

P.T. 34; K.W. 0715120, 0715165, 0785035

National Heart, Lung, and Blood Institute

The Division of Lung Diseases, National Heart, Lung, and Blood Institute (NHLBI), cosponsorship with the AIDS Program, National Institute of Allergy and Infectious Diseases (NIAID), is soliciting proposals from offerors who are willing to cooper as clinical centers in a longitudinal study on the pulmonary complications associated with Human T-Lymphotropic Virus, type III/Lymphotropic-Associated Viru (HTLV-III/LAV) infection. The specific objectives of this program are 1) to coll information on pulmonary complications due to HTLV-III/LAV infection in individua in various transmission categories (risk groups) and 2) to determine the types, incidence, course, and outcome of pulmonary disorders in recently diagnosed patie with acquired immune deficiency syndrome (AIDS), in recently diagnosed (i.e., wit 3 to 6 weeks) AIDS related complex (ARC) patients, and in individuals asymptomatically infected with HTLV-III/LAV.

Physicians who have examined many AIDS patients have the recent impression that a shift is occurring in the types and incidence of pulmonary complications associat with HTLV-III/LAV infection. There appears to be an increased incidence of serio infection with pyogenic bacterium; both pulmonary and extra pulmonary infection w M. tuberculosis has been noted with increased frequency. Nonspecific interstitia pneumonitis appears to be on the rise. Cases of lymphoid interstitial pneumoniti which is diagnostic of AIDS in children under 13 years old who are HTLV-III/LAV antibody positive, are being seen with increased frequency in adults.

Participating clinical centers will be expected to recruit a minimum of 200 participants, age 18 years and older, during a 12 month recruitment period. The distribution of participants should be: 50 AIDS patients, 50 ARC patients and 10 asymptomatic HTLV-III/LAV-infected individuals. Offerors will be expected to provide a plan for evaluating pulmonary status of each study participant and a pl for maintaining contact with participants over the four year recruitment and stud phase of the project. A separate RFP will be issued for the clinical coordinatin center which will be responsible for coordinating the collection, storage, and analysis of data related to the study.

The study will be conducted in three phases. Phase I (6 months) will include the design of the collaborative protocol, manual of operations, and data forms. Phas II will involve the recruitment (1 year) and study and follow-up (3 years) of participants. Phase III (6 months) will be devoted to data analysis.

This announcement is not a Request for Proposals (RFP). It is anticipated that RFP-NHLBI-HR-87-09 will be available on or about January 9, 1987, with proposals on April 6, 1987. Copies of the RFP may be obtained by written requests addresse

Douglas W. Frye, Contracting Officer
for the Division of Lung Diseases
Contracts Operations Branch
National Heart, Lung, and Blood Institute
Westwood Building, Room 654
5333 Westbard Avenue
Bethesda, Maryland 20892

This request should include (3) self addressed mailing labels.

CORONARY HEART DISEASE AND STROKE IN PEOPLE AGED 65 TO 84 YEARS: FIELD CENTERS

RFP AVAILABLE: NIH-NHLBI-HC-87-04

CORONARY HEART DISEASE AND STROKE IN PEOPLE AGED 65 TO 84 YEARS: COORDINATING CENTER

RFP AVAILABLE: NIH-NHLBI-HC-87-11

P.T. 34; K.W. 0715040, 0715200, 0411005, 0607024, 0706030, 0404000

National Heart, Lung, and Blood Institute

The Epidemiology and Biometry Research Program, DECA, NHLBI, seeks a coordinating center and four field centers 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 study will emphasize: (1) the study of established and suspected risk factors that may induce clinically overt disease in an older population; (2) the prediction of clinical disease will be assessed from measures of preclinical disease, such as carotid atheromata measured by ultrasound, left ventricular impairment by echocardiography, and arrhythmias or episodes of myocardial ischemia by Holter monitoring; and (3) the evaluation of participants at frequent intervals for status with respect to concurrent disease, social support networks, stressful life situations, dietary and physical activity, health behaviors, etc. Cohort participants will be examined during the second and fifth years of the six year study, with interval home visits every six months during years two through five. Cohorts must be non-institutionalized and community-based, or representative of a defined population.

In addition to these RFPs for the Coordinating Center and the Field Centers, separate RFPs will be announced in the NIH Guide as they become available for the Lipid and Hemostasis Center, Ultrasound Reading Center, and Echocardiography Reading Center.

This is an announcement of availability of the Request for Proposals (RFP) for the Field Centers. RFP NHLBI-HC-87-04 will be available on or about January 23, 1987, with proposals due March 23, 1987. Four awards are anticipated. Your written request should include three mailing labels, self addressed, and must cite RFP NHLBI-HC-87-04.

This is also an announcement of availability of the Request for Proposals (RFP) for the Coordinating Center. RFP NHLBI-HC-87-11 will be available on or about January 23, 1987, with proposals due March 23, 1987. One award is anticipated. Your written request should include three mailing labels, self addressed, and must cite RFP No. NHLBI-HC-87-11.

Requests for copies of these RFPs 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

HOLDING FACILITY FOR AUTOIMMUNE MICE

RFP AVAILABLE: RFP-NIH-NIAMS-87-1

P.T. 34; K.W. 1002002, 0715015

National Institute of Arthritis and Musculoskeletal and Skin Diseases

The Arthritis and Rheumatism Branch, Division of Intramural Research, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is seeking an organization having the capability to provide a stable environment in a biologically clean holding facility for approximately 4,000 Government-owned autoimmune mice of numerous strains for use by NIAMS investigators in the study of systemic lupus and related autoimmune diseases. The facility must be AAALAC accredited and registered as a research facility with USDA. Care of the mice, and building construction and maintenance shall be in conformance with DHEW Publication No. 77-23, Guide for the Care and Use of Laboratory Animals.

Any organization possessing the capability of performing this service may request copy of the RFP. Requests must be in writing and addressed to:

Patrick M. Sullivan, Contracting Officer
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
Westwood Building, Room 602
Bethesda, Maryland 20892

This acquisition is a 100% Small-Business Set-Aside.

This RFP will be available on or about January 15, 1987, with an anticipated clos date of February 16, 1987. Your written request must include two (2) nonfranked self addressed mailing labels. Telephone requests will not be honored. A reasonable number of the RFP have been prepared and will be issued on an as available basis.

This advertisement does not commit the Government to award a contract.

GASTROINTESTINAL EPITHELIAL CELL CULTURES - SOURCES SOUGHT

P.T. 34; K.W. 0780015, 1002004

National Institute of Diabetes and Digestive and Kidney Diseases

In order to facilitate research on the expression and regulation of various gastrointestinal epithelial cell absorptive, secretory, digestive, endocrine, immune, and other functions, thereby providing a basis for understanding the cellular mechanisms underlying a number of gastrointestinal (including diarrheal) diseases, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), is seeking sources with the capabil to develop and characterize immortalized epithelial (including cryptoid, absorpti secretory, goblet, parietal, endocrine, pancreatic acinar, and Peyer's patch M) c cultures derived from various segments (including small intestine and colon) of t normal gastrointestinal tract of vertebrates. Cancer cell lines with differentia subsets cloned for specific epithelial functions would also be useful in this connection. Awardees of Cooperative Agreements, Research Project Grants, or Research and Development Contracts will be required to submit new long lasting or immortalized gastrointestinal cell lines to the NIH cell culture bank so that the can be made generally available for research.

Sources that believe they have the capability necessary to under take investigati of the type described above should specify the cell culture(s) they are particula interested in and should submit Capability Statements, not exceeding three single-spaced pages, which provide evidence that there are in-house expertise, capability, and facilities for carrying out the proposed investigations.

This announcement is not a Request for Proposals (RFP). There is no commitment b NIDDK to issue a Request for Proposal, but, if such a request is issued, those answering this Sources Sought announcement will be so notified. Three copies of the Capability Statement should be submitted to:

Patrick M. Sullivan, Contracting Officer
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Westwood Building, Room 602
Bethesda, Maryland 20892

Capability Statements must be received no later than close of business, 5:00 (loc time), February 27, 1987.

TARGETING ANTIVIRAL DRUGS TO INFECTED CELLS

RFA AVAILABLE: 87-AI-06

P.T. 34; K.W. 0715120, 0740015, 0740020, 0755025, 0760045

National Institute of Allergy and Infectious Diseases

Application Receipt Date: March 30, 1987

The National Institute of Allergy and Infectious Diseases (NIAID) invites applications for regular research grants to investigate and develop techniques th can be used to deliver antiviral drugs to infected cells. Research efforts to design new or to modify existing potentially effective drugs for the treatment of

AIDS, to increase their permeability across the blood brain barrier, to deliver compounds to the CNS either by modification of the drug or by the use of physical methods for intrathecal therapy and to deliver drugs specifically to cells infected with HTLV-III/LAV/HIV are considered responsive to this RFA.

BACKGROUND

A significant amount of time and effort is required to identify effective antiviral drugs either through screening or targeted development. However, often drugs identified are of limited use because they do not cross the blood brain barrier or the toxicities associated with the drug are too high. The successful development of methods to deliver drugs to the cells infected with the virus will increase the usefulness of a given drug and perhaps decrease the amount of drug required to control the viral infection. At present, research into the development of compounds that cross the blood brain barrier and target HTLV-III/LAV/HIV infected cells needs to be emphasized. Accordingly, the NIAID wishes to invite regular research grant applications in these areas of investigation.

OBJECTIVES AND SCOPE

The NIAID wishes to stimulate research on the delivery of drugs to viral-infected cells. Research efforts to design new or to modify existing potentially effective drugs for the treatment of AIDS, to increase their permeability across the blood brain barrier, to deliver compounds to the CNS either by modification of the drug or by the use of physical methods for intrathecal therapy and to target drugs specifically to cells infected with HTLV/III/LAV/HIV are considered responsive to this RFA. The term "drug" as defined in this RFA encompasses any synthetic or natural chemical or biological reagent that can be used in the treatment of a viral infection. Investigators are encouraged to propose studies that stress innovative approaches to the problem and advance development of currently available methods and techniques. Approaches utilizing ester linkages of carrier groups to antivirals, liposomes, lipophilic carriers, and monoclonal antibodies, are expected. Investigators, however, are not constrained to these for response to this announcement.

INQUIRIES

Additional information and a copy of the full RFA may be obtained from:

John McGowan, Ph.D.
Preclinical Development Program, Treatment Branch
AIDS Program, NIAID, NIH
Westwood Building - Room 753
Bethesda, Maryland 20892
Telephone: (301) 496-0545

MINORITY FAMILIES AND CHILDREN: BEHAVIORAL AND SOCIETAL VARIABLES AFFECTING CHILDREN'S DEVELOPMENT

RFA AVAILABLE: 87-HD-05

P.T. 34, AA, FF; K.W. 0404004

National Institute of Child Health and Human Development

Application Receipt Date: April 15, 1987

The Human Learning and Behavior Branch (HLB) of the Center for Research for Mothers and Children (CRMC), National Institute of Child Health and Human Development (NICHD) is inviting grant applications for the support of re-search on Minority Families and Children: Behavioral and Societal Variables Affecting Children's Development. The purpose of this solicitation is to encourage studies of psychological and societal variables particularly affecting the families of Afro-Americans, Asian-Americans, Hispanic-Americans, and Native-Americans; and their impact on the physical and behavioral development of children from infancy through adolescence.

This RFA is designed to stimulate research in the above populations on family process including commonalities and differences within and between ethnic groups; behavioral development, covering cognitive and social development; and the interaction of health and behavior in development.

It is anticipated that five awards will be made as a result of this announcement through the grant-in-aid mechanism (R01). The FIRST Award mechanism may also be utilized where appropriate.

AIDS, to increase their permeability across the blood brain barrier, to deliver compounds to the CNS either by modification of the drug or by the use of physical methods for intrathecal therapy and to deliver drugs specifically to cells infected with HTLV-III/LAV/HIV are considered responsive to this RFA.

BACKGROUND

A significant amount of time and effort is required to identify effective antiviral drugs either through screening or targeted development. However, often drugs identified are of limited use because they do not cross the blood brain barrier or the toxicities associated with the drug are too high. The successful development of methods to deliver drugs to the cells infected with the virus will increase the usefulness of a given drug and perhaps decrease the amount of drug required to control the viral infection. At present, research into the development of compounds that cross the blood brain barrier and target HTLV-III/LAV/HIV infected cells needs to be emphasized. Accordingly, the NIAID wishes to invite regular research grant applications in these areas of investigation.

OBJECTIVES AND SCOPE

The NIAID wishes to stimulate research on the delivery of drugs to viral-infected cells. Research efforts to design new or to modify existing potentially effective drugs for the treatment of AIDS, to increase their permeability across the blood brain barrier, to deliver compounds to the CNS either by modification of the drug or by the use of physical methods for intrathecal therapy and to target drugs specifically to cells infected with HTLV/III/LAV/HIV are considered responsive to this RFA. The term "drug" as defined in this RFA encompasses any synthetic or natural chemical or biological reagent that can be used in the treatment of a viral infection. Investigators are encouraged to propose studies that stress innovative approaches to the problem and advance development of currently available methods and techniques. Approaches utilizing ester linkages of carrier groups to antivirals, liposomes, lipophilic carriers, and monoclonal antibodies, are expected. Investigators, however, are not constrained to these for response to this announcement.

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John McGowan, Ph.D.
Preclinical Development Program, Treatment Branch
AIDS Program, NIAID, NIH
Westwood Building - Room 753
Bethesda, Maryland 20892
Telephone: (301) 496-0545

MINORITY FAMILIES AND CHILDREN: BEHAVIORAL AND SOCIETAL VARIABLES AFFECTING CHILDREN'S DEVELOPMENT

RFA AVAILABLE: 87-HD-05

P.T. 34, AA, FF; K.W. 0404004

National Institute of Child Health and Human Development

Application Receipt Date: April 15, 1987

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This RFA is designed to stimulate research in the above populations on family process including commonalities and differences within and between ethnic groups; behavioral development, covering cognitive and social development; and the interaction of health and behavior in development.

It is anticipated that five awards will be made as a result of this announcement through the grant-in-aid mechanism (R01). The FIRST Award mechanism may also be utilized where appropriate.

For further information and a copy of the detailed RFA, contact:

Sarah Friedman, Ph.D.
Human Learning and Behavior Branch
National Institute of Child Health and Human Development
Bethesda, Maryland 20892
Telephone: (301) 496-6591

ONGOING PROGRAM ANNOUNCEMENTS

RESEARCH INTO METHODS OF RESEARCH THAT DO NOT USE VERTEBRATE ANIMALS, USE FEWER VERTEBRATE ANIMALS, OR PRODUCE LESS PAIN AND DISTRESS IN VERTEBRATE ANIMALS USED IN RESEARCH

P.T. 34; K.W. 0755020, 0710030, 1002027, 0780015, 0780020

Division of Research Resources

Application Receipt Dates: February 1, June 1, October 1

BACKGROUND

As part of the plan for research into research methods that do not use animals, use fewer animals, or produce less pain and distress in animals used in research, called for in NIH's authorizing legislation, P.L. 99-158, Section 4, the National Institutes of Health invites grant applications for the support of development and validation of research methods promoting these objectives.

Biomedical research cannot be regarded separately from biological research. Applications of basic biology to clinical medicine are often apparent, but cannot, in general, be predicted. Some proposals--for the study of invertebrates, lower vertebrates, microorganisms, cell and tissue culture systems, or mathematical approaches--can be regarded as having the same potential relevance to biomedical research as proposals for work on systems that are phylogenetically more closely related to humans. Experience indicates that information yielded by such systems can contribute substantially to increasing knowledge of human function.

While it is recognized that animals have been and will continue to be essential to the advancement of knowledge in the biomedical sciences, non-animal research methods can and do provide additional opportunities to advance our understanding of basic mechanisms of fundamental biological processes. For example, biological models or model systems derived from or consisting of nonmammalian organisms, or cell and tissue culture systems, may serve to reduce the use of mammals in the early stages of some investigations and may provide insights into mechanisms of biological functions that are more difficult to obtain from studies of whole vertebrate animals. Non-invasive experimental techniques, permitting studies of biological processes in intact animals, can reduce the number of animals needed as multi-step phenomena can be observed within a single subject. Such technologies often permit studies impossible to perform otherwise. Mathematical modeling is another useful investigational strategy when closely coupled to biological experimentation, and there are opportunities for mathematical modeling in many areas of biomedical research.

RESEARCH GOALS

Grant applications are requested for projects that will increase the extent and depth of knowledge needed to develop methods of biomedical research and experimentation that:

- o do not require the use of vertebrate animals
- o reduce the number of vertebrate animals used in research
- o produce less pain and distress in vertebrate animals than methods currently used
- o validate or demonstrate the reliability of non-animal methods
- o develop non-vertebrate animal research methods that have been found valid and reliable

MECHANISM OF SUPPORT

The support mechanism for this program will be the traditional investigator-initiated research project grant. Under this mechanism, the applicant will plan, direct, and carry out the research program. The project period during which the research will be conducted should adequately reflect the time required to accomplish the stated goals and be consistent with the policy for grant support. Support will be provided for up to five years (renewable for subsequent periods) subject to the availability of funds and progress achieved.

Research grant applications may be submitted by both nonprofit and profit-making organizations and institutions, State or local governments and their agencies, and eligible agencies of the Federal Government.

APPLICATIONS AND REVIEW PROCEDURES

Applications in response to this solicitation will be appropriately peer reviewed for scientific and technical merit. They will be judged on the overall scientific merit of the proposed research, potential significance of the research findings, adequacy of methodology, availability of necessary facilities, and the qualifications of the research team. A secondary review for policy and program relevance to the research needs and missions of the Bureau, Institute, or Division to which the proposal is assigned will be made by the respective National Advisory Councils.

Applications will be received by the NIH Division of Research Grants on PHS Form 398, "Application for Public Health Service Grant," in accordance with the usual receipt dates for new applications:

February 1 June 1 October 1

FOR FURTHER INFORMATION CONTACT:

Division of Research Resources
Dr. James D. Willett
Chief, Biomedical Models and Materials Resources Section
Animal Resources Program
Building 31, Room 5B23
Bethesda, Maryland 20892
Telephone: (301) 496-5175

National Cancer Institute
Dr. Michael Boyd
Associate Director for Developmental Therapeutics
Landow Building, Room 5A21B
Bethesda, Maryland 20892
Telephone: (301) 496-8720

National Center for Nursing Research
Dr. Eileen Hasselmyer
Special Assistant to Acting Director
Building 38A, Room 2E17
Bethesda, Maryland 20892
Telephone: (301) 496-0523

National Institute of Allergy and Infectious Diseases
Dr. Luz A. Froehlich
Deputy Director, Extramural Activities Program
Westwood Building, Room 703
Bethesda, Maryland 20892
Telephone: (301) 496-7688

National Institute on Aging
Dr. Dewitt Hazzard
Head, Resource Development, Biomedical Research and Clinical Medicine
Building 31, Room 5C19
Bethesda, Maryland 20892
Telephone: (301) 496-6402

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

National Institute of Child Health and Human Development
Dr. Antonia Novello
Deputy Director
Building 31, Room 2A04
Bethesda, Maryland 20892
Telephone: (301) 496-1848

National Institute of Diabetes and Digestive and Kidney Diseases
Dr. Walter Stolz
Director, Division of Extramural Activities
Westwood Building, Room 657
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Telephone: (301) 496-7277

National Institute of Dental Research
Dr. Marie U. Nylen
Associate Director for Extramural Program
Westwood Building, Room 503
Bethesda, Maryland 20892
Telephone: (301) 496-7723

National Institute of Environmental Health Sciences
Dr. Anne P. Sassaman
Associate Director, Extramural Program
Building 3, Room 301
P.O. Box 12233
Research Triangle Park, North Carolina 27709
Telephone: (919) 541-7723 or (FTS Number) 8-629-7723

National Institute of General Medical Sciences
Dr. David Wolff
Deputy Associate Director for Program Activities
Westwood Building, Room 955
Bethesda, Maryland 20892
Telephone: (301) 496-7063

National Heart, Lung, and Blood Institute
Dr. Amoz I. Chernoff, Director
Division of Blood Diseases and Resources
Federal Building, Room 518A
Bethesda, Maryland 20892
Telephone: (301) 496-4868

National Heart, Lung, and Blood Institute
Dr. Millicent Higgins, Acting Director
Division of Epidemiology and Clinical Applications
Federal Building, Room 212B
Bethesda, Maryland 20892
Telephone: (301) 496-2533

National Heart, Lung, and Blood Institute
Dr. William J. Zukel, Acting Director
Division of Heart and Vascular Diseases
Federal Building, Room 416A
Bethesda, Maryland 20892
Telephone: (301) 496-5656

National Heart, Lung, and Blood Institute
Dr. Suzanne Hurd, Director
Division of Lung Diseases
Westwood Building, Room 6A16
Bethesda, Maryland 20892
Telephone: (301) 496-7208

National Institute of Neurological and Communicative Disorders and Stroke
Dr. Eugene Streicher
Director, Fundamental Neurosciences Program
Federal Building, Room 916
Bethesda, Maryland 20892
Telephone: (301) 496-5745

PANCREATITIS: PATHOGENESIS, DIAGNOSIS, AND THERAPY

P.T. 34; K.W. 0715085, 0745020, 0415000, 0785055, 0760035

National Institute of Diabetes and Digestive and Kidney Diseases

Application Receipt Dates: February 1, June 1, and October 1

PURPOSE

The Pancreas Program of the Division of Digestive Diseases and Nutrition (DDDN) of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports research and related training into the structure, function, and diseases of the exocrine pancreas. Toward this end, this program seeks to expand its support of basic and clinical research and research training in the broad area of the pathogenesis, diagnosis, and treatment of the various diseases constituting human pancreatitis. Accordingly, applications are invited for regular research project grants, program project grants, FIRST awards, career development awards, and postdoctoral fellowships relating but not limited to: (a) the conduct of epidemiological studies to identify those individuals who are at greatest risk for

pancreatic disease and to determine what characteristics (e.g., the roles of diet, alcohol, drugs, exposure to environmental pollutants, and regional factors) predispose certain individuals or groups of individuals to the development of pancreatitis, (b) the development of the ability to safely and conveniently obtain percutaneous or transduodenal biopsy samples of the pancreas from patients with pancreatitis as well as other disorders, (c) a better understanding of the processes involved in the inception and progression of the various types of human pancreatitis, (d) the elucidation of the mechanisms underlying the distant manifestations (e.g., hypovolemia, hypocalcemia, and pulmonary failure) of acute pancreatitis, (e) the development of clinically relevant (i.e., similar to the human disease), simple, inexpensive, noninvasive, and slow to evolve experimental models of the various diseases constituting human pancreatitis, (f) rigorous biochemical studies on the types of inhibitors known or suspected to be present in pancreatic juice from normal man and comparison with those in pancreatic juice from patients with pancreatitis in an attempt to define the breakdown of the cell's first line of defense against premature activation of pancreatic proenzymes, (g) detailed quantitative studies using freeze-fracture electron microscopy of pancreatic tissue afflicted with pancreatitis to determine whether or not tight junctions are primarily or secondarily disrupted, (h) studies of the potential role of the immune system in pancreatitis, (i) the development of precise and convenient diagnostic techniques for the various types of human pancreatitis, and (j) the development of effective methods of prevention and treatment of the various diseases constituting human pancreatitis.

BACKGROUND

Pancreatitis is a general term designating a group of diseases in which the basic lesions are injury of acinar cells and inflammation of the pancreas. Although we know a number of clinical settings which are associated with, and a number of conditions thought to cause pancreatitis, we know almost nothing about its pathogenesis. Moreover, there is lack of agreement regarding the morphological changes which appear during early stages of human acute pancreatitis.

A recent review (M. L. Steer: Workshop on Experimental Pancreatitis. Digestive Diseases and Sciences 30, 575-581, 1985) of the current state of research in experimental pancreatitis and of the possible importance of lysosomal enzymes in the development of pancreatitis indicates that controversy continues to surround the issue of whether basolateral discharge of digestive enzymes occurs in supramaximal stimulation-induced pancreatitis as well as the importance of this phenomenon to the development of pancreatitis. Uncertainties also exist concerning the conditions within the large cytoplasmic vacuoles found during diet- and supramaximal stimulation-induced pancreatitis, leaving open the question of whether or not these conditions would favor trypsinogen activation by cathepsin B. More recently, evidence was provided demonstrating that oxygen-derived free radicals may mediate an early and essential step in the pathogenesis of acute pancreatitis in the isolated, perfused, ex vivo canine pancreas model and suggesting that xanthine oxidase may be the source of their production. Although a large number of animal models of pancreatitis have been reported, the utility of information derived from studies of the animal models has been limited by our ignorance of the extent to which the disease process in animals resembles pancreatitis in humans. Better understanding of the pathogenesis of human pancreatitis should facilitate development of clinically relevant animal models. Other types of systems that could be explored for their potential of being used to establish models of human pancreatic diseases are pancreatic tissues maintained in tissue or organ culture. Overall, however, there is general agreement that great strides in gaining an understanding of pancreatitis have been recently made, and that, to a great extent, this is the result of the availability of experimental models which might be used to evaluate the evolution of pancreatitis at the cellular and the subcellular level as well as models which might be used to evaluate methods of treating pancreatitis. This recent progress suggests that even more important observations may shortly be made and that an effective means of treating and/or preventing this disease may emerge.

Evaluation of the diagnostic accuracy of a symptom, sign, or laboratory test for pancreatitis requires an independent, totally reliable indicator (a "gold standard") of the presence or absence of this condition. For most diseases this gold standard is the presence of appropriate gross or microscopic changes in the diseased organ. Unfortunately, in acute pancreatitis the clinical syndrome is nonspecific, and tissue seldom is obtained for histological verification of disease. In addition, the correlation between the results of a laboratory test and pancreatic histology is far from perfect. As a result, the presence or absence of acute pancreatitis is documented with certainty in only a small percentage of patients in whom this diagnosis is considered. This lack of a certain diagnosis makes it virtually impossible to assess the true diagnostic accuracy of the many tests used for the diagnosis of acute pancreatitis. Knowledge of the pathogenesis of pancreatitis is important, not only in its own right, but it would also serve as a basis for developing a rationale for therapeutic intervention in this disorder and would facilitate development of precise, convenient diagnostic techniques. Precise diagnostic techniques are essential for any clinical trial comparing different

therapies as well as for studies designed to elucidate the mechanism via which various clinical settings or agents cause pancreatitis.

Biopsy of the pancreas has long been regarded as a dangerous procedure because of the risk of producing a pancreatic fistula. Newer techniques like needle-aspiration cytology using thin needles under ultrasonic visualization have minimized this problem. Development of the ability to safely and conveniently obtain percutaneous or transduodenal biopsy samples of the pancreas would allow techniques from various disciplines to be applied to the analysis and characterization of the changes in the pancreas which accompany the onset and propagation of the various disease states. When one considers the advances made possible because of our ability to biopsy the liver or small intestine, it seems likely that equally significant progress would occur as a result of the availability of pancreatic biopsy specimens.

MECHANISMS OF SUPPORT AND REVIEW PROCEDURE

Applications considered appropriate responses to this announcement include the traditional research project grant (R01), the program project grant (P01), the FIRST Award (R29), the Individual National Research Service Award (F32), and the following career development awards: the Research Career Development Award (K04), the Clinical Investigator Award (K08), and the Individual Physician Scientist Award (K11). The specific application forms and kits required in this connection are available in the business or grants and contracts offices of most academic and research institutions or may be obtained from:

Office of Grants Inquiries
Division of Research Grants, NIH
Westwood Building, Room 449
Bethesda, Maryland 20892
Telephone: (301) 496-7441

Applications in response to this announcement will be reviewed on a nationwide basis in competition with other applications and in accordance with the usual National Institutes of Health peer review procedures. The initial review for scientific and technical merit will be by an appropriate study section of either the Division of Research Grants, NIH or the NIDDK; secondary review will be by the National Diabetes and Digestive and Kidney Diseases Advisory Council. Funding decisions will be based upon relative scientific merit, program relevance, and the availability of appropriated funds.

APPLICATION PROCEDURE

Applications will be accepted on an indefinite basis in accordance with the receipt, Initial Review Group, National Advisory Council, and earliest possible beginning dates specified in the pertinent application kits.

On the first (face) page, item 2, of the application, the word "Yes" should be checked and the phrase "RESPONSE TO NIDDK (DDDN) ANNOUNCEMENT ON PANCREATITIS: PATHOGENESIS, DIAGNOSIS, AND THERAPY" should be typed in the space provided. Additionally, a brief covering letter should accompany the application indicating it is being submitted in response to this program announcement.

The original and six copies of the application should be sent or delivered to:

Application Receipt Office
Division of Research Grants, NIH
Westwood Building, Room 240
Bethesda, Maryland 20892

STAFF CONTACT

For further information concerning this announcement and the mechanisms of support for research and training available in this connection, investigators are encouraged to contact:

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This program is described in the Catalog of Federal Domestic Assistance No. 13.848, Digestive Diseases and Nutrition Research. Awards will be made 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 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.

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