NIH Guide
for Grants and Contracts

Vol. 15, No. 6, May 23, 1986

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES

IN THIS ISSUE:

Continued

The NIH Guide is published at irregular intervals to announce scientific initiatives and to provide policy and administrative information to individuals and organizations who need to be kept informed of opportunities, requirements, and changes in grants and contracts activities administered by the National Institutes of Health.

Two types of supplements are published by the respective awarding units. Those printed on yellow paper concern contracts: solicitations of sources and announcement of availability of requests for proposals. Those printed on blue paper concern invitations for grant applications well-defined scientific areas to accomplish specific program purposes.

Have You Moved?
If you present address differs from that shown on the address label, please send your new address to: Grants and Contract Guide Distribution Center, National Institutes of Health, Room B3BN10, Building 31, Bethesda, Maryland 20205, and attach your address label to your letter. Prompt notice of your change of address will prevent your name from being removed from our mailing list.

NOTICE

THE NATIONAL CENTER FOR NURSING RESEARCH

P.T. 34; K.W. 0785130, 0730000, 0745035, 0745055, 0415000

On Friday, April 18, Secretary Otis R. Bowen, M.D. announced the creation of the National Center for Nursing Research (NCNR) as the newest component of the National Institutes of Health (NIH). Doris H. Merritt, M.D., who since August 1978, has been Research Training and Research Resources Officer at the NIH and a Special Assistant to the NIH Director, has been appointed Acting Director of the new Center.

The NCNR research program of grants and awards will support nursing research and research training related to patient care, the promotion of health, the prevention of disease, and mitigation of acute and chronic illnesses and disabilities. In support of studies of nursing intervention, procedures, delivery methods and ethics of patient care, NCNR programs are expected to complement other NIH biomedical research programs.

The Division of Research Grants (DRG) is establishing a Nursing Research Study Section which will deal with the scientific and technical merit review of applications for research projects related to the interest of the NCNR that do not naturally fall within the scientific expertise of the currently chartered DRG Initial Review Groups.

Inquiries concerning the NCNR should be addressed to:

The National Center for Nursing Research
National Institutes of Health
Building 38A - Room B2E17
8600 Rockville Pike
Bethesda, Maryland 20894

Telephone: (301) 496-0526

NOTICE

New NIH Institute Established

P.T. 34; K.W. 0710030

The Health Research Extension Act of 1985 (P.L. 99-158) created a new National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMSD). This institute was formally established on April 8, 1986. Dr. Laurence E. Shulman has been named as Acting Director.

P.L. 99-158 also designated the remaining components of the former National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) as the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDKD). Dr. Pierre F. Renault will continue as Acting Director of the renamed institute.

NOTICE

THE FIRST INDEPENDENT RESEARCH AND TRANSITION (FIRST) AWARD (R-29)

P.T. 34; K.W. 0710030, 0404000, 1014002

Supplemental Information

NATIONAL INSTITUTES OF HEALTH

Item III H in the announcement for the FIRST Award which appeared in the March 28, 1986, issue of the NIH Guide for Grants and Contracts (Vol. 15, No. 4) carried information regarding the restriction of page numbers for a FIRST application. The limit of 20 pages applies to the following portions of the research plan: specific aims, background and significance, preliminary studies and experimental design and methods. The remaining portion of the application is to be prepared in accordance with the specifications shown on PHS 398 (Rev. 5/82), except for appendices. As stated in the Guide announcement, three collated sets of appendix material are to be included with the application.

ERRATUM

NOTICE

AVAILABILITY OF REQUEST FOR GRANT APPLICATIONS: RFA

86-AG-02

FORECASTING LIFE EXPECTANCY AND ACTIVE LIFE EXPECTANCY

P.T. 34; K.W. 0710010, 0413002, 0404007, 1010013

NATIONAL INSTITUTE ON AGING

The fifth sentence in the third paragraph of the above cited Notice, published in the NIH Guide for Grants and Contracts Vol. 15, No.4, March 28, 1986, incorrectly included reference to "program" projects. Only research projects (R01) applications will be considered under the set-aside. The text of the corrected paragraph should read as follows:

MECHANISMS OF SUPPORT

The administrative and funding mechanism to be used to support the studies carried out under this RFA will be the research project grant. The regulations (Code of Federal Regulations, Title 42, Part 52 and Title 45, Part 74) and policies that govern the research grant programs of the Public Health Service will prevail. This RFA is a one time invitation. The duration of proposed projects may be up to five years. The start date for funded projects will be approximately July 1, 1987. A total of $750,000 will be allocated to fund the first year awards, with the actual number of the awards dependent upon the scope and quality of the approved projects. Grant applications will be reviewed as a single competition by an initial review group convened by the NIA Scientific Review Office.

NOTICE

ADAMHA POLICY ON PERIOD OF SUPPORT OF RESEARCH GRANTS

P.T. 34; K.W. 1014002, 0710030

ALCOHOL, DRUG ABUSE, AND MENTAL HEALTH ADMINISTRATION

PURPOSE

The Alcohol, Drug Abuse and Mental Health Administration (ADAMHA) is announcing a goal to increase the proportion of their research grants which are awarded for 4-5 years.

BACKGROUND

Concerns have been expressed by a number of scientists and administrators about the cost of application preparation which is associated with the typical 3 year award. In recent years, about 85% of ADAMHA's regular research grants have been made for project periods of 3 years or less. In FY 1985, only 7% of awards were made for 5 year periods. The purpose of this initiative is to reduce the costs for investigators and the agency associated with preparation and review of frequent applications for grants, and in so doing provide investigators with more time to conduct research and to demonstrate meaningful results.

GOALS

ADAMHA is encouraging more investigators to apply for longer term (4-5 year) research projects. Such support is intended for established investigators who have a proven record of productivity and scientific contribution and for unusually promising newer investigators. Longer term awards are intended for research proposals in an area where the same general line of investigation is likely to be productive for a 4-5 year period. It is expected that investigators applying for more than 3 years of support will describe work proposed in the later years in more general terms than for the first 3 years. However, for these later years, applicants should provide a general outline of anticipated investigations and contingencies based on expected outcomes in the earlier years.

It is anticipated that the most frequent project period will continue to be 3 years. However, ADAMHA wants to significantly increase the submission of applications for longer periods of support, and intends to give favorable consideration to such applications.

REVIEW CRITERIA

Guidelines are being provided to Initial Review Groups (IRGs) concerning the factors to be considered in recommending projects for 4-5 years. The following are the criteria which IRGs will be asked to follow:

o An established track record of productivity and scientific contribution by the principal investigator, or the unusual promise of a newer principal investigator as evidenced by innovative ideas and quality of publications. The record and promise of other key research staff on the project also will be considered.

o Institutional resources sufficient to foster and support the proposed line of research for the full period requested.

o The proposed research of a nature where the same general line of investigation is likely to be productive for the full period of support requested. (In general, less detail will be expected with regard to work planned for the later years of the project, but the Principal Investigator (PI) should outline the general plans for these years.)

As for all projects, any cuts recommended in time and/or amount must be specifically justified.

Projects Requiring Longer Term Support: ADAMHA also welcomes the submission of applications for research projects whose design requires 4-5 years, where such a design is appropriate to the nature of the research. For such applications, investigators should provide the usual level of detail about the proposed research plan for the full period of support requested, and the usual scientific merit review criteria will be used by review groups.

ANNOUNCEMENT

AVAILABILITY OF REQUEST FOR APPLICATIONS: RFA

86-OD-03

ACADEMIC RESEARCH ENHANCEMENT AWARD

P.T. 34,14; K.W. 1200180

NATIONAL INSTITUTES OF HEALTH

Application Receipt Date: September 22, 1986

In its report accompanying the Fiscal Year 1985 appropriation for the National Institutes of Health (NIH), Congress called for an initiative to strengthen the research milieu of non-research-intensive, four-year colleges and universities which provide undergraduate or graduate training for a significant number of our Nation's research scientists. In FY 1985, the NIH made $5,000,000 available for this purpose and was able to award 75 "Academic Research Enhancement Awards" (AREAs). This award is designed to enhance the research environment of educational institutions that have not been traditional recipients of NIH research funds. The award is intended to support new research projects or expand ongoing research activities proposed by faculty members of these institutions in areas related to the health sciences.

Congress has again appropriated funds for the AREA Program for FY 1986. Grant applications for this round are currently undergoing review for scientific merit. Since it is anticipated that additional funds will be available next year, the NIH is inviting grant applications for the FY 1987 competition for AREA grants.

Eligibility requirements of the AREA Program include the following:

1. Applicant Institutions

   (a) Must be a domestic institution offering baccalaureate or advanced degrees in the sciences related to health.

   (b) Have received an NIH Biomedical Research Grant (BRSG) in no more than three of the six fiscal years from FY 1981 through FY 1986. Health professional schools (e.g., schools of medicine, dentistry, nursing, osteopathy, pharmacy, veterinary medicine, public health, allied health and optometry) are eligible if they meet both criteria above, as are officially discrete campuses of a university. Multiple applications proposing different research projects may be submitted by an applicant institution.

2. Applicant Principal Investigators

(a) Must not have active research grant support (including an AREA) from either NIH or the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA) at the applicant institution at the time of award of an AREA grant.

(b) May not submit a regular NIH or ADAMHA research grant application for essentially the same project as a pending AREA application.

(c) Are expected to conduct the majority of their research at their own institution, although limited access to special facilities or equipment at another institution is permitted.

(d) May not be awarded more than one AREA grant.

Those in doubt about eligibility should consult their institution's office of sponsored research, or the NIH Office of Special Programs and Initiatives (Building 31, Room 1B54, NIH, Bethesda, MD 20892, 301/496-1968).

Funding decisions will be based on the proposed research project's scientific merit and relevance to NIH programs, and the institution's contribution to the undergraduate preparation of doctoral-level health professionals. Among projects of essentially equivalent scientific merit and program relevance, preference will be given to those submitted by institutions that have granted baccalaureate degrees to 25 or more individuals who, during the period 1977-1986, obtained academic or professional doctoral degrees in the health related sciences.

The AREAs are awarded on a competitive basis. Applicants may request support for up to $50,000 in direct costs (plus applicable indirect costs) for a period not to exceed 24 months. Although this award is non-renewable, it will enable qualified individual scientists within the eligible institutions to receive support for feasibility studies, pilot studies and other small-scale research projects preparatory to seeking more substantial funding from the regular NIH research grant programs.

Applications for this award will be accepted under the regular application submission procedures of the Division of Research Grants (DRG) of NIH. Grant applications must be prepared and submitted on PHS 398 grant application forms. An abbreviated format and simplified instructions will be provided for use in preparing these applications. The receipt date is **September 22, 1986.**

Those individuals and institutions meeting eligibility requirements and wishing to receive further information and/or application materials should write to:

AREA
Office of Grants Inquiries
Division of Research Grants
National Institutes of Health
Westwood Building - Room 449
Bethesda, Maryland 20892

ANNOUNCEMENT

AVAILABILITY OF REQUEST FOR APPLICATIONS: RFA

86-HL-21-H

BYPASS ANGIOPLASTY REVASCULARIZATION INVESTIGATION (BARI) DATA COORDINATING CENTER

P.T. 34; K.W. 0755015, 1010013, 0785055, 0715040

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Application Receipt Date: August 22, 1986

The Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute (NHLBI), announces the availability of a request for applications (RFA) on the above program.

The Division invites applications for a Data Coordinating Center to participate with NHLBI in the design and performance of a collaborative randomized clinical trial to assess the relative efficacy of percutaneous transluminal coronary angioplasty and coronary artery bypass graft surgery in patients who require invasive therapy and have coronary anatomy suitable for either procedure. The program will include randomized studies in well-defined subsets of patients with symptomatically severe coronary artery disease. The cooperative agreement, an assistance mechanism, will be used to support this study. It is anticipated that one Data Coordinating Center will participate in BARI, subject to the availability of funds. The proposed program will support the Data Coordinating Center for a period of eight years. Among the disciplines and skills appropriate for this research program are those of Biostatistics, Epidemiology, Data Management, Cardiovascular Research, and Clinical Trials.

The RFA will be released on May 15, 1986. Requests for copies of the RFA should be addressed to the following individual.

Thomas L. Robertson, M.D.
Chief, Cardiac Diseases Branch
Federal Building - 3C06
7550 Wisconsin Avenue
Bethesda, Maryland 20892
Telephone: (301) 496-1081

ANNOUNCEMENT

AVAILABILITY OF REQUEST FOR COOPERATIVE AGREEMENT APPLICATIONS

86-CA-10

NATIONAL COLLABORATIVE DIAGNOSTIC IMAGING TRIAL PROJECTS

P.T. 34; K.W. 0706030, 0755015, 0710030, 0715035, 1010013, 0735015

NATIONAL CANCER INSTITUTE

Application Receipt Date: September 24, 1986

The Division of Cancer Treatment (DCT) of the National Cancer Institute (NCI) invites applications for Cooperative Agreement for NATIONAL COLLABORATIVE DIAGNOSTIC IMAGING TRIAL PROJECTS (NCDITP). The objectives of the present proposal are to conceive new approaches for the development and implementation of national cooperative trials carried out by multiple institutions using this approach to develop new algorithms for the appropriate sequential use of the most advanced imaging procedures to diagnose, stage and monitor malignant disease.

The present RFA Announcement is for a single competition with a specified deadline of September 24, 1986 for receipt of application.

BACKGROUND

The decades of the 1970s and 1980s have been characterized by spectacular technical advances in medical imaging, particularly those applied to tumor definition and characterization. These technologies have now developed to the stage where a clear identification of the relative roles of each diagnostic modality in the diagnosis and staging of cancer is warranted. To date, most comparative studies evaluating imaging technologies have been based at a single institution and have involved small numbers of cases making their results often equivocal and not applicable in large scale patient care settings.

GOALS AND SCOPE

The objective of this RFA is to support multi-center cooperative clinical trials to determine the most effective imaging procedures required to stage and monitor carcinoma of the prostate and lung.

This program is described in the Catalog of Federal Domestic Assistance No. 13.395, Cancer Treatment Research. Awards will be made under the authority of Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended; 42 USC 282) and administered under PHS grant policies and Federal Regulations 42 CFR Part 52 and 45 CFR 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

A. Requirements for Operations Center and Data Management Center:

The Operations Center shall have expertise in the design, and coordination of multi-disciplinary, multi-modal cooperative clinical trials and capability to develop scientifically valid results in the most efficient manner.

It also shall have the capacity to develop and implement a structure for a Cooperative Group (CG), including: a) criteria for membership of an Executive Committee, b) a Quality Assurance Committee, and c) a Protocol and Research Strategy Committee which will assume responsibility for the development of randomized studies and set the priorities for protocol development, as well as the capability for monitoring performance of studies.

The Statistical and Data Management Center shall have expertise in the design of guidelines for statistically valid studies planned for multi-institutional trials in Diagnostic Imaging, including setting standards for patient evaluability according to protocol documents and professional personnel with expertise in data management and analysis and the ability to participate in cooperative clinical trials to provide centralized statistical services.

B. Group Participants:

Group participants must demonstrate a commitment to participate in multi-institutional protocols and availability of facilities equipped to carry out various technologies: e.g., MRI, CT, etc., professional personnel and sufficient number of patients to conduct cooperative imaging trials.

MECHANISM OF SUPPORT

The mechanism for this award is Cooperative Agreement. NCI anticipates the formation of a single group with separate funding for the Operations and/or Statistical Center(s) and Individual Institutions for a period of 4 years. The initial year is expected to start in 1987 with an estimated total budget of $600,000. This award is contingent upon the availability of funds.

STAFF CONTACT

A copy of the complete RFA describing the research goals and scope, the nature of NCI staff participation, the review criteria and method of applying can be obtained by contacting:

Dr. Matti Al-Aish, Deputy Chief
Diagnostic Imaging Research Branch
Radiation Research Program
National Cancer Institute
National Institutes of Health
Landow Building/Room 8C09
Bethesda, MD 20892

Telephone: (301) 496-9531

ANNOUNCEMENT

SOLID TUMOR CYTOGENETICS AND CANCER DIAGNOSIS

P.T. 34; K.W. 1002015, 1002019, 0715035, 0745020, 1002004

NATIONAL CANCER INSTITUTE

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

The Division of Cancer Biology and Diagnosis (DCBD) of the National Cancer Institute (NCI) invites grant applications from interested investigators to expand the understanding of cytogenetic changes occurring in human solid tumors. Chromosome analysis is being employed increasingly in the diagnosis and evaluation of hematopoietic tumors. However, there are insufficient data available to determine whether chromosome analyses will be equally useful in the case of solid tumors. Studies of solid tumors have been hampered by technical difficulties, particularly in the area of cell culture. Improvements of existing technology are required before the data necessary to determine the value of chromosome analyses can be collected.

This announcement is intended to encourage and facilitate development of collaborations between cytogeneticists and researchers with expertise in cell culture. It is hoped that such joint efforts will result in improved ability to examine the chromosomes in human solid tumors; it then should be possible to increase the database and hopefully to gain new insights into the chromosome alterations associated with tumor development and progression in these tumors. This is an area of special importance to the National Cancer Program.

BACKGROUND INFORMATION

There has been continuing discussion in the scientific literature concerning the potential importance of chromosome analysis in cancer detection, diagnosis and/or prognosis. Attempts are underway to correlate observed chromosome alterations with the tumor stage or the particular tumor type. There is growing evidence that cytogenetic abnormalities have prognostic importance in some leukemias. Chromosome studies on melanocytic lesions of different stages of malignancy demonstrate some consistent karyotypic changes. To date, most cytogenetic studies of solid tumors have been small and many more cases need to be examined before their utility can be confirmed. In addition, different tumor types must be examined to determine whether the observed cytogenetic changes are unique or common. Unique changes would be important for distinguishing subtypes of a given cancer (e.g. the different types of lung cancer) or for establishing the tissue origin of metastatic tumors. However, it is possible that some

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This program is described in the Catalog of Federal Domestic Assistance No. 13.394, Cancer Detection and Diagnosis Research. 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 Regulation 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.

alterations are common to the early stages of progression of a number of different kinds of tumors and although these alterations may not be unique to a particular tumor, they may be of value in grading the malignancy or in evaluating its metastatic potential.

The ability to grow solid tumor tissue in vitro must be improved in order to facilitate karyotype analysis. The collection of karyotype data from solid tumors has been seriously hampered by the inability to obtain sufficient suitable metaphases from these tumors. An additional problem has been the development of methods that assure that the population of cells dividing in culture is either representative of the population in the original tumor or representative of a critical subset of cells within the tumor. Further research is required to address these problems.

OBJECTIVES AND SCOPE

It is the intent of this announcement to encourage studies which will lead to improved ability to examine chromosomes in human solid tumors and will add to the data base required to determine the potential importance of cytogenetic analysis of these tumors to cancer diagnosis. Since at least a brief period of in vitro culture is required to obtain suitable metaphases from solid tumors, there is inevitable cell selection within the cultured population. Investigations are encouraged to address such questions as: How can it be determined that the cells being examined are the significant ones? How can tissue preparation techniques and growth media be improved to assure growth of tumor cells and suppression of fibroblasts and other normal cells associated with the tumor? Collaborations between investigators working on the development of culture techniques and cytogeneticists examining solid tumors should be considered.

Laboratories that are already involved in studies of human solid tumors are also encouraged to expand their studies to include cytogenetic analyses. Investigators studying cytogenetics of hematopoietic tumors who have access to solid tumor tissue are urged to consider including solid tumor studies. Applications for supplements to ongoing NCI grants can be submitted in response to this announcement in order to facilitate such expansions; the period of award for supplemental applications will be concurrent with the ongoing grant.

Applications received in response to this announcement will be reviewed by an appropriate peer review group of the NIH. Recommendations of the peer review group will be considered by the National Cancer Advisory Board. The scientific merit evaluation of each application will consider those factors used in evaluation of traditional NIH research grant applications including:

1 Assessment of the potential importance of the proposed research to the objectives described in this announcement.

2 Scientific merit of the proposed approach, including the adequacy and quality of the methodological approach and the research design. Familiarity with the proposed techniques should be demonstrated, e.g., by the presentation of preliminary results.

3 Demonstration of availability and access to appropriate clinical materials.

4 Expertise and qualifications of the Principal Investigator and proposed staff and/or collaborators.

5 Adequacy of the facilities and resources.

6 Appropriateness of the requested budget relative to the work proposed.

METHOD OF APPLYING

Applications should be submitted on form PHS 398. Application kits are available at most institutional business offices; from the Division of Research Grants, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland, 20892; or from the NCI Program Director named below.

The conventional presentation for grant applications should be utilized. Supplemental applications should include a statement describing how the supplement will influence the specific aims, experimental design and methods of the current grant.

The present announcement is open to all interested investigators. Support for these awards is through the traditional NIH grant-in-aid and is governed by the policies applicable to such grants. Applications (including supplemental applications) will be accepted in accordance with the usual NIH receipt dates for new applications: October 1, February 1 and June 1. Be sure to type **"Solid Tumor Cytogenetics and Cancer Diagnosis"** in Section 2 on the front page of the application form. The original and six 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

INQUIRIES

Inquiries concerning this announcement are encouraged and should be directed to:

Sheila E. Taube, Ph.D.
Diagnosis Branch
Division of Cancer Biology and Diagnosis
National Cancer Institute
Westwood Building - Room 10A15
Bethesda, Maryland 20892

In order to alert Program Staff to the submission of proposals in response to this announcement, applicants are requested to send a brief letter of intent to Dr. Taube. A letter of intent is not binding, is not required for application, and will not enter into the review of a subsequent application.

ANNOUNCEMENT

CONTROL OF CELL PROLIFERATION IN SENESCENT CELLS

P.T. 34; K.W. 0710010, 1002004, 1002008, 1002019

NATIONAL INSTITUTE ON AGING

INTRODUCTION

The National Institute on Aging (NIA) was established in 1974, to conduct and support biomedical, behavioral, and social research and training related to the aging process and the diseases and other special problems and needs of the aged. Consistent with this mandate the Molecular Biology and Genetics subprograms of the Molecular and Cellular Biology Program support research on the molecular and genetic mechanisms of aging. The purpose of this announcement is to encourage further research and training activities using modern tools of molecular biology and genetics to elucidate the molecular bases of cellular aging processes.

BACKGROUND

Current evidence suggests that quiescent and senescent cells contain factors which inhibit DNA replication and cell proliferation. It is even more apparent that cells respond to and contain factors which induce or stimulate DNA replication and cell proliferation. These factors are thought to be proteins, induced by genes whose expression is controlled in a cell cycle-dependent manner, presumably during traverse of the G1 phase of the cell cycle.

It is presumed that initiation of DNA repliction is carefully controlled in normally growing cells. Naturally-occurring DNA rearrangements, or rearrangements induced by external stimuli, may alter this control, as well as control of gene expression in significant ways. Such alterations may accumulate as time passes, and they may contribute causally to the aging process.

GOALS AND SCOPE

The goal of this announcement is to encourage research on the control of DNA replication and cell proliferation, with particular emphasis on processes related in a causal way to senescence in mammals. Such studies could lead to understanding the reasons why senescent cells can no longer be stimulated to divide, why cells die, and the relationship between these events and organ and organismal senescence.

SPECIFIC OBJECTIVES

The NIA seeks research and training grant applications to test hypotheses and elucidate mechanisms related to the following areas:

- o Identification, characterization, and role of factors which are found predominately in senescent cells and are involved in control of DNA replication and cell proliferation.

- o Identification, characterization, and role of factors that are involved in control of DNA replication and cell proliferation, and are specifically absent or present in low amounts in senescent cells.

- o Control of gene expression in the G1 phase of the cell cycle, particularly for genes whose products are the factors referred to above.

- o Mechanism of turnover of factors referred to above.

- o Identification and characterization of DNA rearrangements which directly affect any of the above processes.

- o Differences between quiescent and senescent cells with regard to proliferative potential, with particular emphasis on where and how the arrest of DNA replication occurs.

Although studies with human cells and tissues are preferred, use of other vertebrates may be desirable where shorter lifespans and better genetic systems are an advantage. Therefore, the NIA supports several colonies of animals and an Aging Cell Repository for use in aging research. Applicants interested in using these resources should contact the following persons:

Contact person for Rats and Mice:
Ms. Jane Soban
Molecular and Cellular Biology Branch
Building 31 - Room 5C19
National Institute on Aging, NIH
9000 Rockville Pike
Bethesda, Maryland 20892

Telephone: (301) 496-6402

Contact person for Cultured Cells:
Dr. Arthur E. Greene
Aging Cell Repository
CORIELL Institute for Medical Research
Camden, New Jersey 08103

MECHANISMS OF RESEARCH AND RESEARCH TRAINING SUPPORT

The primary mechanisms for support of this program are:

- o Research grant.

- o Program project grant, involving several projects with a common focus.

- o Postdoctoral fellowship.

Additional mechanisms for support are:

- o Research career development awards, for up to $40,000 per year for five years, salary support only.
- o Physician scientist award for clinically trained investigator; ceiling $40,000 per year for salary and up to $20,000 per year for supplies for five years.
- o Institutional training grant.

Potential applicants should contact NIA staff for information and advice (see below).

REVIEW PROCEDURES AND FUNDING POLICY

According to standard referral guidelines, the NIH Division of Research Grants will assign all applications to appropriate NIH study sections for initial scientific review, and to the appropriate Institute or Division for final review by its National Advisory Council or Board. Applications submitted in response to this program announcement will compete with all NIA grant applications for funding consideration. No set aside money is available for these applications.

METHOD OF APPLYING

Use the appropriate NIH research or research training grant application kits. If your institution does not have them, copies may be obtained by writing:

Office of Grant Inquiries
Division of Research Grants
National Institutes of Health
Bethesda, Maryland 20892

Telephone: (301) 496-7441

Please type the phrase **"NIA Genetics Program"** on line 2 of the face page of the application. Forward the application to:

Division of Research Grants
National Institutes of Health
Westwood Building - Room 449
5333 Westbard Avenue
Bethesda, Maryland 20892

Potential applicants interested in obtaining further information can call:

Dr. Huber R. Warner
Chief, Molecular and Cellular Biology Branch
National Institute on Aging, NIH
Building 31 - Room 5C19
Bethesda, Maryland 20892

Telephone (301) 496-6402

ANNOUNCEMENT

HOST INTESTINAL MUCOSAL RECEPTORS AND ENTEROTOXIN AND MICROBIAL ADHERENCE IN INFECTIOUS DIARRHEAS

P.T. 34; K.W. 0715125, 1003002, 1002019, 0710070, 1002027, 0760075

**NATIONAL INSTITUTE OF DIABETES, AND DIGESTIVE AND KIDNEY DISEASES
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES**

I. PURPOSE

As a part of their mission to support research and related training into the normal function and the diseases of the gastrointestinal tract and the pathogenic mechanisms of infectious diarrheal diseases, the Gastrointestinal Digestive and Immunology Program (P.A. 5A-1) of the Division of Digestive Diseases and Nutrition (DDDN) of the National Institute of Diabetes, and Digestive and Kidney Diseases (NIDDK) and the Enteric Diseases Program of the Microbiology and Infectious Diseases Program (MIDP) of the National Institute of Allergy and Infectious Diseases (NIAID) desire to expand their support of research, both basic and clinical, and training in the broad area of mediation of enterotoxin and microbial adherence in infectious diarrheas by receptors on the intestinal mucosal surface of the host. Accordingly, applications are invited for regular research project grants, program project grants, First Independent Research Support and Transition (FIRST) Awards, career development awards, and postdoctoral fellowships (Individual National Research Service Awards). Applications should be related , but not limited to studies of: (a) the structure, (b) specificity, (c) biological function, (d) distribution, (e) genetic control, (f) age of development, and (g) role in enterotoxin and microbial binding of the host receptors; (h) mode of action and (i) fate (viz., internalization, metabolism, inactivation, etc.) of enterotoxin after binding to receptor; (j) the intracellular events (e.g., adenylate or guanylate cyclase activation and involvement of calcium, calmodulin, and protein kinase) leading to the secretion of water and electrolytes following binding of the enterotoxin to the receptor; (k) the relation of binding to the host cell and surface recognition to uptake, invasion of the intestinal epithelium, and destruction of the

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These programs are described in the Catalog of Federal Domestic Assistance No. 13.848, Digestive Diseases and Nutrition Research and 13.856, Microbiology and Infectious Diseases Research. Awards will be made under the authority of the Public Health Service Act, Section 487, 42 USC 288, and administered under PHS grant policies and Federal Regulations 42 CFR Part 66. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

infecting agents by host intestinal defense mechanisms; and (l) receptor and enterotoxin analog therapy. It is hoped that these studies would hopefully serve as a basis for developing a rationale for therapeutic intervention in diarrheas from infectious causes. Thus, since toxins bind to receptors on the mucosal cells to stimulate water and electrolyte secretion, competitive blocking of the receptor site should prevent toxin-mediated diarrhea. This could be accomplished by administering a large oral dose of a false toxin to bind receptors and prevent binding of the real toxin. Alternatively, large doses of toxin receptor could be given orally to bind the toxin. In this case, less toxin is available to bind receptors on the intestinal mucosal cells.

II. BACKGROUND

Diarrhea from infectious causes still contributes considerably to neonatal and infantile morbidity and mortality in much of the world; moreover, acute diarrheal disease is a major cause for sick leave and loss of productivity, even in Western societies. Chronic diarrheal diseases, often manifested as states of intestinal malabsorption, though less common, are important because of their long-term morbidity in the young. Causative bacteria (e.g., Vibrio cholerae, Escherichia coli, Clostridium difficile, Shigella dysenteriae 1, Campylobacter jejuni, Yersinia enterocolitica, Vibrio parahemolyticus, and Aeromonas hydrophila), viruses (e.g., rotaviruses), and parasites (e.g., Giardia lamblia and Entamoeba histolytica) have been recognized, but additional infectious agents await identification.

It has recently become clear that a number of infectious diseases of the gastrointestinal tract are mediated by attachment of microorganisms and enterotoxins to the intestinal mucosal surface of the host. Evidence suggests that, in each case, mucosal adherence is mediated by a specific "binding site" - "receptor site" interaction between surface structures elaborated by bacteria and naturally occurring elements of the host mucosal surface, respectively. Rapid progress has been made in localizing the colonization factor antigens (adhesins) of bacteria to a class of hair-like appendages termed pili or fimbriae. In contrast, very little progress has been made in defining the specific receptors on the intestinal surface of the host which mediate adherence. The best molecular candidates for the host receptors for pili are the carbohydrate portions of mucosal glycolipids or glycoproteins, molecules present in the apical epithelial cell membranes, but also abundant in the intestinal mucous gel. With regard to enterotoxins, it is now well established that the glycolipid, GM1 ganglioside, is a specific receptor for cholera toxin. The toxin exerts its effect after first binding to the oligosaccharide moiety of this ganglioside on the surface of the cell. Certainly a great deal of additional work needs to be done in defining the mucosal receptors for enterotoxins, bacteria, viruses, and protozoa. For example, investigations are needed addressing the following questions: (a) Do these receptors share other important digestive or absorptive functions? (b) At what age do they develop and what is their distribution in the host? (c) Are bacterial/enterotoxin-host cell interactions modified by alteration of the receptors? (d) What is the relation of binding to the host cell and surface recognition to uptake, invasion of the intestinal epithelium, or destruction of the infecting agents by host defense mechanisms? (e) To what extent do receptor-adhesin reactions determine the selection of the normal flora? (f) What is the role of mucus in the balance between colonization and clearance, and does the mucus share receptors with the epithelial cells? (g) Is it possible to either protect

against or treat diarrheas from infectious causes by developing appropriate receptor site analogs to either prevent colonization or dislodge the causative microorganisms from the intestinal mucosal surface of the host?

III. 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 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
National Institutes of Health
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 (NIH) 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 NIADDK/NIAID; secondary review will be by the National Arthritis, Diabetes, and Kidney Diseases Advisory Council/National Allergy and Infectious Diseases Advisory Council. Funding decisions will be based upon relative scientific merit, program relevance, and the availability of appropriated funds.

IV. 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 NIADDK (DDDN/5A-1)/NIAID ANNOUNCEMENT ON INTESTINAL RECEPTORS AND ENTEROTOXIN AND MICROBIAL ADHERENCE IN INFECTIOUS DIARRHEAS"** should be typed in the space provided.

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

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

V. 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 either:

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