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. 25 - JULY 24, 1987

Vol. 16, No. 25, July 24, 1987

NOTICES

DATED ANNOUNCEMENTS (RFPs AND RFAs AVAILABLE)

NOTICES

NIH REGIONAL WORKSHOPS ON IMPLEMENTATION OF THE PHS POLICY ON HUMANE CARE AND USE OF LABORATORY ANIMALS

P.T. 42; K.W. 1014002, 1014003, 0201011

National Institutes of Health

The National Institutes of Health, Office for Protection from Research Risks, is continuing to sponsor a series of workshops in implementing the revised Public Health Service Policy on the Humane Care and Use of Laboratory Animals. The workshops are open to institutional administrators, members of animal care and use committees, laboratory animal veterinarians, investigators and other institutional staff who have responsibility for high-quality management of sound institutional animal care and use programs.

Date: September 14-15, 1987

Location: Minneapolis, Minnesota

Contact:

Cynthia S. Gillett, DVM
Research Animal Resources
Division of Comparative Medicine
Box 351 UMHC
University of Minnesota
Minneapolis, Minnesota 55455
Telephone: (612) 624-4625

Date: January 28-29, 1988

Location: Albuquerque, New Mexico

Contact:

Ms. Rynda Gibbs
University of New Mexico School of Medicine
Continuing Medical Education
815 Vassar N.E.
Albuquerque, New Mexico 87131
Telephone: (505) 277-3942

Other workshops are being planned and will be announced in future issues of the NIH Guide for Grants and Contracts.

For additional information contact:

Ms. Roberta Garfinkle
Executive Assistant for Animal Welfare Education
National Institutes of Health
Office of Protection from Research Risks
Building 31, Room 4B09
Bethesda, Maryland 20892

DATED ANNOUNCEMENTS (RFPs AND RFAs AVAILABLE)

CORONARY HEART DISEASE AND STROKE IN PEOPLE AGED 65 TO 84 YEARS - ULTRASOUND READING CENTER

RFP AVAILABLE: NHLBI-HC-87-06

P.T. 34; K.W. 0715040, 0785055, 0607024

National Heart, Lung, and Blood Institute

The Epidemiology and Biometry Research Program, DECA, NHLBI, seeks an ultrasound reading center 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 ultrasound reading center will develop a protocol for collection of ultrasound data at the four field centers and perform precise measures of carotid artery lumen and lesion features.

In addition to this RFP for the Ultrasound Reading Center, separate RFPs have been announced for the Coordinating Center, the Field Centers, the Echocardiography Reading Center and the Central Blood Analysis Laboratory.

RFP NHLBI-HC-87-06 for the Ultrasound Reading Center will be available on or about August 28, 1987, with proposals due on or about October 28, 1987. One award is anticipated. Your written request should include three mailing labels, self-addressed, and must cite RFP No. NHLBI-HC-87-06.

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, MD 20892

MANIPULATION OF THE SUPPRESSOR ARM OF THE IMMUNE RESPONSE DIRECTED TOWARDS SUCCESSFUL HUMAN IMMUNOTHERAPY

RFA AVAILABLE: 87-CA-30

P.T. 34; K.W. 0745045, 0710060, 0755015

National Cancer Institute

Application Receipt Date: November 16, 1987

The Division of Cancer Treatment of the National Cancer Institute (NCI) invites grant applications from interested investigators for basic and applied studies to investigate manipulation of the suppressor arm of the immune response directed toward successful human immunotherapy.

BACKGROUND INFORMATION

The immune system is highly complex, composed of different types of cells located in various central and peripheral lymphoid organs. The complex immunologic network can affect, among other responses, the growth of cancer cells. In certain animal models, tumors can be demonstrated to be antigenic and to be rejected on the basis of immune responses to these antigens. This potentially beneficial host response can, however, be inhibited by the development of suppressor functions, which may be present as part of the normal physiologic process by which immune responses are regulated. Thus, a tumor which could otherwise be rejected escapes immunologic elimination because of the normal inhibitory regulatory system.

Several groups have identified the subtypes of suppressor lymphocytes in animal models and have demonstrated that the suppressor arm of the immune response can be abolished or diminished with significant anti-tumor effects. As elegant as these studies are, however, they are, nevertheless, very difficult to translate into practical therapy for cancer patients. It is very hard to establish whether individual tumors in humans are antigenic, a critical point since it is principally with antigenic tumors that specific suppressor modulation might be expected to be successful. The detailed mode of action of certain agents such as cyclophosphamide which affect the suppressor arm of the immune response are poorly understood. Convincing in vitro systems that measure suppressor effects in cancer tumor systems are rare, and most of the animal models that measure suppressor cell phenomena do so by in vivo measurement of progressive tumor growth. Finally, in animal models, the inhibition of suppressor cell function can only be carried out in a precisely timed manner with regard to the growth of tumor, a restriction not easily possible in humans. Despite all these difficulties, attempts to regulate the suppressor phase of the immune response in humans so as to achieve a successful anti-tumor effect, should be investigated.

RESEARCH GOALS AND SCOPE

The goal of this research is to obtain information from preclinical systems that would lead to successful manipulation of the suppressor arm of the immune response so as to enhance a destructive immunologic attack on malignant tumors. New agents that can decrease suppressor cells should be sought.

Known examples of such agents include cyclophosphamide, cimetidine, cyclooxygenase inhibitors and deoxyguanosine. The cellular and molecular mechanisms of action of such agents should be explored. For reasons which are unclear, suppressor T cell subsets appear to be more susceptible than effector T cell subsets to a number of these agents. Also desirable would be the establishment of innovative animal models to explore the role of suppressor cells in cancer biology. This could include therapy of ultraviolet (UV) radiation-induced and carcinogen-induced autochthonous tumors. For example, UV radiation in vivo suppresses the immune response systemically. Investigation of the mechanism(s) by which this occurs could provide information about how suppressor cells are produced in vivo. In order to be responsive to this RFA, the application should include some experiments which are designed to demonstrate cancer regression in a therapy model. Although the major intent of this RFA is to encourage preclinical modeling studies, appropriately designed clinical trials, based on preclinical data, would also be accepted.

MECHANISM OF SUPPORT

Support for this program will be through the traditional research grant (R01). Policies that govern research grant programs of the National Institutes of Health will prevail.

REVIEW PROCEDURES AND CRITERIA

Applications in response to this announcement will be reviewed in accordance with the usual Public Health Service peer review procedures for research grants, i.e., an appropriate review panel consisting primarily of non-Federal employees convened by the Division of Extramural Activities, NCI. Secondary review for programmatic relevance will be by the National Cancer Advisory Board. The present RFA announcement is for a single competition with a specified deadline of November 16, 1987 for receipt of applications. The intent is to fund 4-5 projects. All applications will be evaluated by a single review panel in accordance with the review criteria. Future renewal applications will not compete for earmarked funds. Instead, all renewal applications will be considered as unsolicited grant applications which will compete with all other unsolicited applications received by NIH.

Review criteria include significance and originality of the research goals and approaches and responsiveness to the goals of the RFA; feasibility of the research and adequacy of experimental design; training, experience, and research competence of the investigator(s); adequacy of available facilities; provision for the adequacy of protection of human subjects, the humane care of animals and appropriateness of the requested budget to the work proposed. The application will be evaluated also for responsiveness to the research goals of the RFA by the Biological Response Modifiers Program, NCI. Applications which are judged as unresponsive to the RFA will be considered with other unsolicited grant applications reviewed during the next NIH review cycle.

Requests for copies of the RFA in its expanded form should be addressed to:

Dr. Ira Green
Biological Resources Branch
BRMP, DCT, NCI-FCRF
Building 426, Room 1
Frederick, MD 21701-1013
Telephone: (301) 698-1098

Applications must be submitted using Form 398 (Rev. 9/86). The RFA label contained in the application kit must be affixed to the bottom of the face page of the original copy of the application. Failure to use this label could result in delayed processing and review of your application.

IMMUNOLOGIC INVESTIGATION OF MULTI DRUG-RESISTANCE OF NEOPLASTIC CELLS

P.T. 34; K.W. 0745005, 0710070

RFA AVAILABLE: 87-CA-28

National Cancer Institute

Application Receipt Date: November 16, 1987

The Division of Cancer Treatment of the National Cancer Institute (NCI) invites grant applications from interested investigators for basic and applied studies for immunologic investigation of multi-drug resistance of neoplastic cells.

BACKGROUND INFORMATION

Cytotoxic chemotherapy is a major form of clinical cancer treatment, and much progress has been made using chemotherapeutic agents. Nevertheless, the emergence of drug-resistant cancer cells during the course of chemotherapy continues to be a major problem. During the past 10 years, a new system, termed multi-drug cross resistance (MDR), has been defined which, in part, explains a major aspect of the drug resistance of cancer cells. When a tumor cell becomes resistant to one class of drug, usually a natural product, the same cell also demonstrates resistance to another class of unrelated drugs, including synthetic compounds. This type of resistance is due to the increased cell membrane expression of a 170,000 dalton glycoprotein which controls the permeability and efflux of drugs from the cell such that cells with a large amount of this protein are able to expel the drug at a faster rate. The protein has been called the P-glycoprotein (P-170). The gene for P-170 has been cloned and the amino acid sequence of the protein is known. Exactly how the presence of increased amounts of P-170 in the cell membrane of resistant cells leads to decreased drug concentration within the cell remains to be fully understood.

Recently, several groups have produced monoclonal antibodies to P-170. These antibodies can be used to identify cells and tissues bearing increased amounts of P-170 and to affect the function of P-170.

RESEARCH GOALS AND SCOPE

The goal of this research is to develop immunologic methods that will lead to a further understanding of the mechanism of action of P-170 and to interfere with its function on cancer cells with the long-term aim of producing favorable clinical therapeutical effects.

Studies are encouraged which will: (1) produce new monoclonal antibodies (MoAbs) against P-170; (2) identify the functional domains of P-170 by production of monoclonal antibodies to polypeptides from different domains of the molecule and testing of these antibodies for effectiveness in inhibiting growth of multi-drug resistant cells and drug binding or drug efflux from cells; (3) use monoclonal antibodies to study receptor function of P-170; here the fate of the drug P-170 conjugate, exocytosis, coated pit localization, breakdown of the conjugate and P-170 recycling should be examined; (4) to investigate how other drugs, e.g., Ca channel blocking agents which can partially overcome MDR interact with P-170; e.g., will certain MoAbs block the association between Ca channel blocking agents and P-170?; (5) to use MoAbs to establish if P-170 molecules exist as a family of molecules; (6) to use MoAbs to inhibit growth of human drug-resistant xenografts in a suitable nude mouse model system; (7) use MoAbs to screen tumor tissues to correlate elevated levels of P-170 with drug resistance in patients; (8) to test P-170 as a target for therapy with MoAbs coupled to toxins or to I131 in vitro and in animal models with the ultimate aim of use in patient therapy; and (9) to develop T-cell and other types of cell-mediated immunity to P-170 bearing cells in animal models and in vitro.

MECHANISM OF SUPPORT

Support for this program will be through the traditional research grant (R01). Policies that govern research grant programs of the National Institutes of Health will prevail.

REVIEW PROCEDURES AND CRITERIA

Applications in response to this announcement will be reviewed in accordance with the usual Public Health Service peer review procedures for research grants, i.e., an appropriate review panel consisting primarily of non-Federal employees convened by the Division of Extramural Activities, NCI. Secondary review for programmatic relevance will be by the National Cancer Advisory Board. The present RFA announcement is for a single competition with a specified deadline of November 16, 1987 for receipt of applications. The intent is to fund 3-5 projects. All applications will be evaluated by a single review panel in accordance with the review criteria. Future renewal applications will not compete for earmarked funds. Instead, all renewal applications will be considered as unsolicited grant applications which will compete with all other unsolicited applications received by NIH.

Review criteria include significance and originality of the research goals and approaches and responsiveness to the goals of the RFA; feasibility of the research and adequacy of experimental design; training, experience, and research competence of the investigator(s); adequacy of available facilities; provision for the adequacy of protection of human subjects, humane care of animals and appropriateness of the requested budget to the work proposed. The application will be evaluated also for responsiveness to the research goals of the RFA by the Biological Response Modifiers Program, NCI. Applications which are judged as unresponsive to the RFA will be considered with other unsolicited grant applications reviewed during the next NIH review cycle.

Requests for copies of the RFA in its expanded form should be addressed to:

Dr. Ira Green
Biological Resources Branch
BRMP, DCT, NCI-FCRF
Building 426, Room 1
Frederick, MD 21701-1013
Telephone: (301) 698-1098

Applications must be submitted using Form 398 (Rev. 9/86). The RFA label contained in the application kit must be affixed to the bottom of the face page of the original copy of application. Failure to use this label could result in delayed processing and review of your application.

PROTECTION OF BONE MARROW AGAINST THE EFFECTS OF CYTOTOXIC DRUGS AND X-IRRADIATION

RFA AVAILABLE: 87-CA-29

P.T. 34; K.W. 0705005, 0755020, 0785190, 0745005

National Cancer Institute

Application Receipt Date: November 16, 1987

The Division of Cancer Treatment of the National Cancer Institute (NCI) invites grant applications from interested investigators for basic and applied studies to investigate protection of bone marrow against the effects of cytotoxic drugs and X-irradiation.

BACKGROUND INFORMATION

One of the limiting features of cancer treatment using standard cancer chemotherapy and X-irradiation is damage to the bone marrow leading to the absence of peripheral blood and tissue leukocytes necessary for host defense against infectious agents. In addition, such damage to bone marrow causes failure of RBC and platelet production. Various agents protect the bone marrow against some of these deleterious effects. Recent preliminary studies with cytokines such as IL-1, G-CSF, GM-CSF, IL-2 and gamma interferon have indicated that these can also protect against the detrimental effects of X-irradiation and of chemotherapy. The detailed mechanism of action and full potential of these agents are still to be explored.

RESEARCH GOALS AND SCOPE

To develop basic preclinical information that will aid in the development of clinical use of bone marrow protecting agents in cancer therapy. This RFA is intended to foster research in animal models to explore these questions. Models in which normal animals or tumor-bearing animals are treated with standard anti-cancer treatment and then treated with bone marrow protecting agents at various times relative to the standard therapy would provide useful information prior to human use of such strategies. Detailed studies of peripheral blood and organ counts of various hematopoietic cell types would be indicated. Also, colony-forming abilities of cells contained within bone marrow and other blood-forming organs should be performed. The above could also be integrated with in vitro models of hematopoiesis, such as Dexter and/or Witte-Whitlock cultures. Such cultures could also be employed to study effects of lymphokines and/or other bone marrow protecting agents at a cellular and molecular level on hematopoiesis and on stromal cells and their interaction with hematopoietic progenitor cells. Considering that many patients who receive cancer therapy die as a result of infectious disease, the possible effects of bone marrow protecting agents, in particular lymphokines such as the CSFs, on infectious disease could also be studied in the above mentioned animal models.

Also encouraged would be the study of combinations of known lymphokines and CSFs and other protecting agents, and the discovery of entirely new lymphokines and biologic response modifiers that might mediate such effects. The discovery of any defined agent of any kind that could have similar protective effects on bone marrow would be highly desirable. Finally, since other rapidly proliferating tissue, such as cells of the gastrointestinal tract, is also damaged by cancer chemotherapy and X-irradiation, the protective effects of the above agents or of other agents could be explored in this regard.

While exploring mechanisms of protective action, it is extremely important in these applications that endpoints measuring anti-cancer effects should also be included.

MECHANISM OF SUPPORT

Support for this program will be through the traditional research grant (R01). Policies that govern research grant programs of the National Institutes of Health will prevail.

REVIEW PROCEDURES AND CRITERIA

Applications in response to this announcement will be reviewed in accordance with the usual Public Health Service peer review procedures for research grants, i.e. an appropriate review panel consisting primarily of non-Federal employees convened by the Division of Extramural Activities, NCI. Secondary review for programmatic relevance will be by the National Cancer Advisory Board. The present RFA announcement is for a single competition with a specified deadline of November 16, 1987 for receipt of applications. The intent is to fund 3-5 projects. All applications will be evaluated by a single review panel in accordance with the review criteria. Future renewal applications will not compete for earmarked funds. Instead, all renewal applications will be considered as unsolicited grant applications which will compete with all other unsolicited applications received by NIH.

Review criteria include significance and originality of the research goals and approaches and responsiveness to the goals of the RFA; feasibility of the research and adequacy of experimental design; training, experience, and research competence of the investigator(s); adequacy of available facilities; provision for adequacy of protection of human subjects, the humane care of animals and appropriateness of the requested budget to the work proposed. The application will also be evaluated for responsiveness to the research goals of the RFA by the Biological Response Modifiers Program, NCI. Applications which are judged as unresponsive to the RFA will be considered with other unsolicited grant applications reviewed during the next NIH review cycle.

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Dr. Ira Green
Biological Resources Branch
BRMP, DCT, NCI-FCRF
Building 426, Room 1
Frederick, MD 21701-1013
Telephone: (301) 698-1098

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EVALUATION OF IMPACT OF EARLY CANCER DETECTION: RETROSPECTIVE STUDIES

RFA AVAILABLE: 87-CA-31

P.T. 34; K.W. 0745020, 0745055, 1010013

National Cancer Institute

Application Receipt Date: October 23, 1987

The Division of Cancer Prevention and Control (DCPC) of the National Cancer Institute (NCI) invites grant applications from investigators interested in elucidating one or more intermediate end-points through analyses of existing data to enable the evaluation and to assess the extent of benefit of early cancer detection.

Intermediate end-points are needed that can be evaluated rapidly and reliably and which have a known link to the subsequent development of cancer. These end-points will enable NCI to evaluate the impact of prevention and early cancer detection research without the need for long term follow-up and high cost associated with randomized clinical trial depending solely on mortality as an outcome.

The scope of this RFA is limited to the analyses of existing data bases in populations that have been exposed to various screening and health maintenance procedures with information concerning early detection, diagnosis, and patient follow-up.

It is the intent of this RFA to identify intermediate end-points that can be used to assess the contributions of early cancer detection, whether initiated by patient or physician.

Applicants are encouraged to submit a letter of intent and consult with NCI program staff before submitting an application because of the need for a clear understanding of the cancer control research issues involved and to facilitate planning for the review of applications.

Nonprofit and for profit institutions within the United States are eligible to apply for project periods up to two years. It is anticipated that a maximum of four awards will be made as a result of this RFA.

Copies of the complete RFA may be obtained from:

Bill Bunnag, Ph.D.
Program Director,
Early Detection Branch, CCO, DCPC
National Cancer Institute, NIH
Blair Building, Room 7A-05
Bethesda, Maryland 20892-4200
Telephone: (301) 427-8708

Applications must be submitted using Form 398 (Rev. 9/86). The RFA label contained must be affixed to the bottom of the face page of the original copy of the application. Failure to use this label could result in delayed processing and review of your application.

SPECIALIZED CENTERS OF RESEARCH IN: CORONARY AND VASCULAR DISEASES; HEART FAILURE; OR CONGENITAL HEART DISEASE

RFA AVAILABLE: 87-HL-26-H

P.T. 04, 34; K.W. 0715040, 0710030

National Heart, Lung, and Blood Institute

Application Receipt Date: May 16, 1988

The Division of Heart and Vascular Diseases of the National Heart, Lung, and Blood Institute (NHLBI), NIH announces the availability of a Request for Applications (RFA) for Specialized Centers of Research (SCOR) in Coronary and Vascular Diseases; Heart Failure; or Congenital Heart Disease. Copies of the RFA and Instructions for the Preparation of Applications are available from staff of the NHLBI.

NHLBI currently supports nine Ischemic Heart Disease SCORs. The Institute, with the advice and concurrence of the National Heart, Lung, and Blood Advisory Council, the Cardiology Advisory Committee, and the research community, now plans to broaden the scope of these SCORs. This is not intended to de-emphasize research on ischemic heart disease, but rather to apply the advantages of the SCOR mechanism to other areas of cardiovascular disease. The renewal of the SCOR program will be focused in the following cardiovascular disease areas:

1 Coronary and Vascular Diseases

2 Heart Failure

3 Congenital Heart Disease

The program is open to all investigators. All applicants must propose both basic and clinical research, and the research activities of an individual SCOR application must focus on only one of the three areas of cardiovascular disease, although a given institution may submit applications in more than one area. It is anticipated that approximately nine SCORs will be funded under this RFA. The requirements and formats for applications submitted in response to the announcement and copies of the RFA may be obtained from:

John Fakunding, Ph.D.
or Constance Weinstein, Ph.D.
Cardiac Diseases Branch
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
Federal Building, Room 3C06
Bethesda, Maryland 20892
Telephone: (301) 496-1081

Applications must be submitted using Form 398 (Rev. 9/86). The RFA label contained in the application kit must be affixed to the bottom of the face page of the original copy of the application. Failure to use this label could result in delayed processing and review of your application.

PATHOGENESIS OF INTESTINAL DYSFUNCTION IN AIDS

RFA AVAILABLE: 87-DK-09

P.T. 34; K.W. 0715120, 0715085, 0785165, 0710030

National Institute of Diabetes and Digestive and Kidney Diseases

Application Receipt Date: November 23, 1987

PURPOSE

The Division of Digestive Diseases and Nutrition (DDDN) of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) invites investigator-initiated applications for regular research project grants involving multi-disciplinary basic and clinical research aimed at elucidating the pathogenesis of intestinal dysfunction in the Acquired Immunodeficiency Syndrome (AIDS). These studies should provide important information concerning the mechanisms of disease progression in AIDS and begin to delineate the strategies that will be needed to manage and treat this disease effectively.

BACKGROUND

In AIDS research to date, the primary emphasis has been the detection, identification, and characterization of the viral causative agent. However, the gastrointestinal manifestations of AIDS are severe and, of these, the wasting syndrome is the one most closely correlated with subsequent death.

There is a fundamental interrelationship between gastrointestinal dysfunction and the wasting syndrome in AIDS. Immune dysfunction results in antigen and pathogen adherence and penetration into the mucosa, chronic viral and mycobacterial infections, lymphoproliferation, and a possible autoaggressive reaction. The resulting extensive histologic damage in the intestinal tract of AIDS patients leads to nutrient malabsorption, increased losses of proteins and other nutrients, and systemic immune stimulation from luminal antigens. Consequently, malnutrition results, including deficiencies of essential micronutrients as well as substrates and energy to support immune responses. Thus, there is a negative feedback of malnutrition on the immune deficiency, and, presumably, a self-perpetuating cycle ensues, which leads to an observed lack of intestinal tissue repletion and consequent terminal course, even in the absence of further specific complications. It is conceivable, therefore, that interruption of this purported vicious cycle by, for example, tissue repletion via total parenteral nutrition might affect morbidity and mortality and would be an important advance in the treatment of AIDS.

Study of the gastrointestinal tract is relevant to studies of immunodeficiency states, since the intestine acts both as a barrier against the environment and as the sole organ to provide nutrition to the body. It is the largest lymphoid organ in the body, and lymphoid cells comprise about 25 per cent of the wet weight of the mucosa. Intestinal function is impaired in other immune deficiencies. Loss of mucosal immunity should lead to increased uptake of antigens into the body and increase the burden on the systemic immune system. This factor may be relevant to the consideration of secondary immune stimulation in promoting AIDS. Since systemic hyporesponsiveness (tolerance) is a function of intestinal lymphoid cells, immune dysfunction with loss of tolerance also may promote secondary immune stimulation.

Abnormalities among T-lymphocyte subsets in the circulation have been reported in homosexual men with AIDS. Many of these individuals also have impaired T-lymphocyte function as assessed by responses to T-cell mitogens or skin test antigens. Whether or not parallel abnormalities in immune function exist in the intestinal mucosa is not known. However, a significant decrease in mucosal T lymphocytes of the helper/inducer phenotype and a decrease in the "helper/suppressor" T-cell ratio in the small intestine of homosexual men with AIDS has been recently reported. In these studies, parallel abnormalities were not found among healthy homosexual men, although the same individuals had abnormal helper/suppressor T-cell ratios in the periphery. One might, therefore, speculate that the abnormalities in intestinal mucosal T cells in subjects with AIDS may be accompanied by a parallel defect in mucosal immune function. Such a defect may render these individuals more susceptible to the persistent and opportunistic enteric infections that occur in AIDS.

An exciting new area of investigation is the finding that neuropeptides, including vasoactive intestinal peptide, substance P, and somatostatin, that are present in the intestine can modulate immune function, including IgA synthesis in a dose-dependent manner, and that receptors for these neuropeptides are found on lymphocytes. Because the concentration of neuropeptides in the mucosa is much higher than in the blood, it is possible that they may be important immunoregulatory factors. This may be of importance for future clinical studies involving AIDS patients in that neuropeptide regulation of immunity in the intestine could modulate inflammatory intestinal diseases or may influence mucosal defense mechanisms, thereby preventing pathogen adherence and penetration, preventing intestinal damage, or facilitating intestinal tissue repletion. Furthermore, the development of pharmacologic agents to modulate the effects of neuropeptides on the mucosal immune system will be of interest as the mechanisms whereby neuropeptides modulate intestinal immune or inflammatory processes are delineated.

OBJECTIVES AND SCOPE

The Gastrointestinal Immunology and Digestion Programs of this Division desire to stimulate support of multidisciplinary basic and clinical research aimed at examining the causes and consequences of intestinal dysfunction and their response to treatment of the AIDS syndrome. Toward this end, applications will be invited for regular research project grants relating but not limited to: (a) studies of the severity and course of malnutrition and its relationship to the timing of death and to the observed immune deficiency, (b) the characterization of the intestinal injury that occurs in patients with AIDS, the examination of its development from infectious and noninfectious factors, and the determination of the relationships between intestinal injury and dysfunction, (c) the determination of the mechanisms of intestinal maldigestion and malabsorption in AIDS and their response to treatment of selected aspects of the syndrome, (d) investigation of intestinal mucosal immune function in AIDS, (e) the determination of the intestinal epithelial portals of entry (including mechanisms of adherence and penetration) in AIDS of the viral causative agent and opportunistic pathogens, and (f) the development of strategies for treating patients with AIDS using a combination of treatments effective against both the viral causative agent and opportunistic pathogens, correction of nutritional deficiencies, and immunomodulatory agents. The abnormalities of gastrointestinal function in AIDS are certainly complex and, although not the primary cause, they could play a major role in the course and clinical outcome of the disease. The proposed studies should provide information which might be important in devising strategies to treat this disease effectively.

MECHANISM OF SUPPORT

Support for this initiative will be through the grant-in-aid and will be governed by the current policies of grant programs of the National Institutes of Health. Applications may be submitted for traditional research project grants (R01s) only. Although plans for Fiscal Year 1988 include $2.8 million for the total (direct and indirect) costs of this initiative, the funding of applications submitted in response to this RFA is contingent on the actual availability of funds and receipt of applications deemed worthy of support by the accepted NIH peer review procedure. It is anticipated that ten to fourteen awards will be made for up to five years under this program. Since a variety of approaches would represent valid responses to this announcement, it is anticipated that there will be a range of costs among individual awards.

APPLICATION AND REVIEW PROCEDURES

Applications in response to this RFA will be reviewed for scientific and technical merit by an initial review group which will be convened by the Division of Extramural Activities, NIDDK, solely to review these applications. Upon receipt, applications will be evaluated for their responsiveness to the objectives of this RFA. If an application is judged unresponsive at this stage, the applicant will be contacted and given an opportunity to withdraw the application or to have it considered for the regular research grant program of the NIH. Should the proposal submitted in response to the RFA be substantially similar to a research application already under consideration by the NIH, the applicant will be asked to withdraw either application. Simultaneous submission of identical applications will not be allowed.

Funding decisions will be based on Initial Review Group and the National Diabetes and Digestive and Kidney Diseases Advisory Council recommendations and relevance to the Objectives and Scope of the RFA. Applicants should request a start date of July 1, 1988.

The RFA label available in the 9/86 revision of Application Form 398 must be affixed to the bottom of the face page. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review.

For further information and copies of the complete RFA, please contact:

G.G. Roussos, Ph.D.
Director
Pancreas Program, and Gastrointestinal Digestion and
Immunology Programs, DDDN/NIDDK
National Institutes of Health
Westwood Building, Room 3A-18A
Bethesda, Maryland 20892
Telephone: (301) 496-7121

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