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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. 18, No. 31
September 8, 1989

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DATED ANNOUNCEMENTS (RFPs AND RFAs)

ONGOING PROGRAM ANNOUNCEMENTS

PRESOLICITATION: INTERNATIONAL COLLABORATIONS IN AIDS RESEARCH

RFA: 89-AI-21

P.T. 34; K.T. 0715008, 0710070, 0411005, 0760003, 0710030

National Institute of Allergy and Infectious Diseases

Anticipated RFA Availability Date: November 1, 1989
Anticipated Application Receipt Date: March 30, 1990

INTRODUCTION

The purpose of this announcement is to alert the scientific community to the proposed issuance of a Request for Applications (RFA) for international collaborations in AIDS research.

RESEARCH GOALS AND SCOPE

The National Institute of Allergy and Infectious Diseases plans to expand its current effort in international health by encouraging and strengthening scientific linkages between U.S. and foreign investigators to develop research units of excellence in locations experiencing large numbers of persons with health problems due to infection with the human immunodeficiency virus.

The proposed initiative will permit a wide range of investigations including study of the natural history of HIV infection, identification of risk groups and risk behaviors associated with transmission, evaluation of the immunological parameters that affect susceptibility to infection among the uninfected and infectivity among the infected, investigation of the routes of transmission in perinatally acquired infection, and identification of early biological or clinical markers of HIV infection and HIV disease in adult and pediatric cases.

MECHANISM OF SUPPORT

This proposed RFA would be funded as a National Institutes of Health (NIH) program project grant. Only domestic institutions are eligible to apply. In 1988, five International Collaborations in AIDS Research (ICARS) were awarded to establish collaborative research centers in countries with high levels of HIV prevalence, including two in Latin America and three in East and Central Africa. The proposed initiative would fund 1-3 additional ICARS for up to 5 years each, at a cost of approximately $500,000 each, per year. In the final selection, preference may be given to projects which expand the geographic spread and distribution of NIH-funded activities, as well as to those located in geographic areas of special interest to the Institute, and where at least 70 percent of the project funds will be used to develop research units in the host country.

To be considered, applications must include evidence of host country approval of the collaboration.

INQUIRIES

Because establishment of international collaborations are anticipated to require several months of negotiations, applicants are urged to commence discussions as soon as possible. Please direct inquiries and requests for information to:

Amy R. Sheon, M.P.H.
Epidemiology Branch
Division of AIDS
National Institute of Allergy and Infectious Diseases
6003 Executive Blvd.
Rockville, Maryland 20892
Telephone: (301) 496-6177

A copy of the RFA, when available, can be obtained by sending two self-addressed mailing labels to Ms. Sheon.

BETA-ADRENERGIC MODULATION OF AIRWAY FUNCTION

RFA AVAILABLE: NIH-89-HL-17-L

P.T. 34; K.W. 0705065, 1002034, 0760050, 0765035, 1002004

National Heart, Lung, and Blood Institute

Application Receipt Date: March 19, 1990

The Division of Lung Diseases of the National Heart, Lung, and Blood Institute (NHLBI) invites grant applications for studies aimed at elucidation of the cellular and molecular mechanisms by which the beta-adrenergic receptor or the beta-adrenergic cascade regulates airway function in health and disease. The primary objective of this special grant program is to stimulate cellular and molecular biologic approaches to delineate the mechanisms regulating beta-adrenergic function in normal airways and its perturbation in disease. Applications received in response to this request will be considered for a single competition.

BACKGROUND

Various neurotransmitters, hormones, and inflammatory mediators exert profound effects on airway smooth muscle tone by interacting with cell surface receptors such as the beta-adrenergic receptor, thereby initiating signals that can affect the physiological control of diverse processes and ultimately modify cell function. However, our understanding of the molecular and cellular mechanisms regulating beta-adrenergic receptor function in airway smooth muscle cells and other target cells in the airways (e.g., submucosal glands, airway epithelium, mast cells, and other inflammatory cells) is far from complete. Knowledge of this receptor function is fundamental to improving our understanding of the cellular and molecular events mediating airway smooth muscle tone and the mechanism underlying smooth muscle contraction and relaxation.

Current evidence suggests that a defect in the beta-adrenergic receptor system could be a contributory factor in the development of asthma. Diminished beta-adrenergic sensitivity in bronchial smooth muscle, mucous glands, and mucosal blood vessels has been proposed to lead to an imbalance in the autonomic control of airway diameter. Although a cause and effect relationship has not been established, asthmatics do exhibit a diminished response to beta-adrenergic stimuli in airway smooth muscle. However, the basic cellular and molecular mechanisms underlying this altered adrenergic responsiveness observed in association with severe persistent asthma are still unclear.

OBJECTIVES AND SCOPE

The overall objective of this program is to encourage studies which will provide fundamental insights into the cellular and molecular mechanisms regulating beta-adrenergic modulation of airway function under normal and pathologic conditions. Applications should clearly define the rationale, background, and specific aims of the proposed studies, and relate them to the mechanisms underlying beta-adrenergic receptor modulation of airway function in health and disease.

MECHANISM OF SUPPORT

The support mechanism for this program will be the traditional, individual research grant. Although approximately $1,200,000 for this program is included in the financial plans for fiscal year 1990, award of grants is contingent upon receipt of funds for this purpose. All current policies and requirements that govern the research grant programs of the National Institutes of Health will apply to grants awarded under this RFA. Applications must be received by March 19, 1990. An application not received by this date will be considered ineligible. Awards will be made to foreign institutions only for research of very unusual merit, need, and promise, and in accordance with Public Health Service Policy governing such awards.

REVIEW PROCEDURES

All applications submitted in response to this RFA will be evaluated for scientific and technical merit by an initial review group, which will be convened for this purpose, by the Division of Extramural Affairs, NHLBI.

METHOD OF APPLYING

Prospective applicants are asked to submit a letter of intent that includes a descriptive title and the names of any other participating institutions or investigators. This letter should be received no later than January 15, 1990. Requests for copies of this announcement may be directed to:

Susan P. Banks-Schlegel, Ph.D.
Airways Diseases Branch
Division of Lung Diseases, NHLBI
National Institutes of Health
Westwood Building, Room 6A15
Bethesda, Maryland 20892
Telephone: (301) 496-7332

NATIONAL COOPERATIVE NATURAL PRODUCTS DRUG DISCOVERY GROUPS

RFA AVAILABLE: 89-CA-17

P.T. 34; K.W. 0740020, 0755020, 0755025, 1003012, 0715035

National Cancer Institute

Letter of Intent Date: October 27, 1989
Application Receipt Date: December 11, 1989

In FY 1983 and 1984, the National Cancer Institute (NCI) requested applications for National Cooperative Drug Discovery Groups (NCDDG) whose goal was the discovery of improved cancer treatment on the basis of novel mechanism of drug action (NIH Guide for Grants and Contracts Vol. 12, No. 7, July 1983, and Vol. 13, No. 9, August 3, 1984). In 1986 the program requested applications focused on exploitation of specific and unique characteristics of lung and colon cancer (NIH Guide for Grants and Contracts Vol. 15, No. 20, October 3, 1986). The NCDDG approach to modern anticancer treatment discovery was broadened further in August 1987 by RFAs inviting applications for the creation and evaluation of both general mechanism of action based and specific disease-oriented anticancer treatments as well as for the development of innovative preclinical models for determining antitumor selectivity. The National Cooperative Natural Products Drug Discovery Groups (NPDDGs) were added in 1988 to further broaden the base of the program and to enhance discovery of novel drug chemotypes.

SUMMARY

The NCI announces the availability of a Request for Applications (RFA) for the funding of NPDDGs to stimulate the scientific community to select and isolate on a rational basis, new potential anticancer treatments from natural sources and to evaluate them in preclinical models designed to select those with the most favorable prognosis for clinical usefulness. This program is designed to assist leading investigators in diverse scientific disciplines to interact as a unit, regardless of their individual institutional affiliations or prior direct involvement in cancer related research. The purpose is to mobilize, with NCI support, the outstanding talents required for exploitation and extrapolation of leads from fundamental studies to the discovery of improved anticancer treatment. An NPDDG is envisioned as being composed of a Principal Investigator and a number of Program Leaders who will conduct interdependent and synergistic preclinical laboratory programs to identify and isolate novel anticancer leads from natural sources, conduct preclinical tasks required to select materials worthy of development based on activity in pertinent laboratory models as perceived by the Group, and provide the basis for identifying new agents and strategies for development to clinical trial. An NPDDG may be made up of scientists in academic, non-profit research, and commercial organizations.

Awards will be made as cooperative agreements. Assistance via cooperative agreement differs from all research grants in that the cooperative agreement funding mechanism anticipates substantial NCI staff participation during performance. However, the applying Group must define its objectives in accord with its own interests and perceptions of approaches to the discovery of new models. The role of NCI as a member of the Group is described in the RFA. Essentially, the extramural NCI staff concerned with the administration of grants and contracts will apply its experiences and appropriate resources to facilitate and stimulate the realization of Group objectives. The active participation of industry is encouraged because it will allow this segment of the scientific community to contribute its considerable intellectual and material resources.

The Principal Investigator's (PI's) institution will be responsible for the Group's application. Awards will be made to the applicant institution on behalf of the Group as a whole and not to individual Laboratory Programs within the Group. The PI's institution will provide a Central Operations Office for the Group and will be responsible for the performance of the entire Group and be accountable for the funds awarded.

NCI plans to make multiple awards for project periods of up to five years and has set aside three million dollars for the initial year's funding.

The RFA label obtained from the NCI staff person named below or from grant application Form PHS 398 (Revised 10/88) must be affixed to the bottom of the face page. Failure to use this label could result in delayed processing of your application such that it may not reach the review committee in time for review.

For further information and a copy of the RFA contact:

Matthew Suffness, Ph.D.
Program Coordinator, NPDDGs
Executive Plaza North, Suite 832
Grants and Contracts Operations Branch
Developmental Therapeutics Program
Division of Cancer Treatment
National Cancer Institute
Bethesda, Maryland 20892

MECHANISMS OF PROTEASE INHIBITOR ANTICARCINOGENESIS

RFA AVAILABLE: 89-CA-18

P.T. 34; K.W. 0715035, 0760035, 0745027, 0755020, 0760013

National Cancer Institute

Application Receipt Date: December 1, 1989
Letter of Intent Receipt Date: November 1, 1989

INTRODUCTION

For many years evidence has accumulated that protease inhibitors can suppress both transformation in cell culture and tumorigenesis in animals. Transformation suppression has been shown in several different in vitro systems employing a variety of inducing agents such as x-rays and UV light, polycyclic aromatic hydrocarbons, 4-nitroquinoline oxide, beta propiolactone, N-methyl-N'-nitro-N-nitrosoguanidine, and steroid hormones. Some interpret these results to mean that different carcinogens induce similar carcinogenic processes involving at least one critical cellular proteolytic enzyme which is susceptible to protease inhibitor suppression. Among the inhibitors effective in vitro have been the small peptide microbially-derived inhibitors, for example, the endopeptidases leupeptin, antipain, and chymostatin; large polypeptide vegetable-derived inhibitors such as Bowman-Birk inhibitor (BBI), chick pea chymotrypsin inhibitor, potato chymotrypsin inhibitor-1; and small, chemically-synthesized compounds such as tosyl-phenylalanine-chloromethylketone (TPCK) and tosyl-L-lysine-chloromethylketone (TLCK). Some evidence exists that protease inhibitors which inhibit the protease chymotrypsin are the most effective in suppression of malignant transformation. It is noteworthy that treatment of cells in culture with low concentrations of some protease inhibitors has an irreversible inhibitory effect on the transformation process, even when added to cultures for short time periods; and that transformation inhibition is still observable when the inhibitor is added to the cultures long after carcinogen exposure.

In vivo studies also have shown or suggested that several types of protease inhibitors can suppress tumorigenesis in animals induced by a variety of carcinogens, in a number of organ systems, and in several species. These studies include suppression of two-stage skin papilloma formation and carcinogenesis in mice (TLCK, TPCK, leupeptin, and soybean diets rich in protease inhibitors), dimethylhydrazine-induced mouse colon tumorigenesis (epsilon-aminocaproic acid, leupeptin, and a crude extract of BBI), x-ray- and chemically-induced breast cancer in rats (soybean diets, leupeptin), dimethylbenzanthracene-induced cheek pouch carcinomas in hamsters (soybean extract enriched in BBI), and genetically-determined, spontaneous hepatocellular carcinomas in inbred, C3H mice (soy-protein concentrate).

Epidemiologic data from a number of population studies have shown that vegetarians and populations consuming large amounts of vegetables have lower tumor risks for a number of organ sites. Many vegetables contain protease inhibitors which could contribute to the lowered incidences observed. A new study on Seventh Day Adventist populations (Cancer, 61, 2578-2585, 1988) indicates that high legume consumption (such as beans, peas, and lentils) and dried fruit is associated with highly protective relationships to pancreatic cancer risk. Legumes are a known rich source of protease inhibitors.

The present Request for Applications (RFA) is for a single competition with a deadline of December 1, 1989, for receipt of applications and November 1, 1989, for receipt of letters of intent. Applications should be prepared and submitted in accordance with the aims and requirements described in the complete RFA document which may be obtained from the program director listed in INQUIRIES below.

Research conducted under this RFA will seek to expand knowledge and understanding of protease inhibitors in the prevention/suppression of experimental carcinogenesis. Specifically, this RFA seeks innovative approaches and basic studies directed at the elucidation of protease inhibitor mechanisms of action in anticarcinogenesis and antitransformation.

The intended research would encompass both in vitro and in vivo systems, and would be confined to investigations employing known, well-characterized models of carcinogenesis/transformation, or to biological systems in which elucidation of basic protease inhibitor mechanisms of action would be expected to contribute to understandings important for anticarcinogenesis. In this latter instance, it is the responsibility of the applicant to elaborate the rationale for the relevance of the intended research to anticarcinogenic mechanisms of action. Examples of studies (by no means inclusive) are: (1) investigations on the identification and characterization of the target molecules significant to the anticarcinogenic action of protease inhibitors; (2) studies on protease inhibitor suppression of oncogene expression in appropriate model systems; (3) investigations on the role of protease inhibitors in suppression of activated oxygen species employing model systems of significance to anticarcinogenesis; and (4) possible preventive interactions, as well as possible side-effect-producing interactions, of protease inhibitors directly or indirectly with host immune or endocrinological systems, including possible interactions with autocrine or paracrine systems of control involving growth factors.

MECHANISM OF SUPPORT

This RFA will use the National Institutes of Health (NIH) traditional research program grant (R01). Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. Except as stated in this RFA, awards will be administered under PHS grants policy as stated in the Public Health Service Grants Policy Statement, DHHS Publication No. (OASH) 82-50,000, revised January 1, 1987.

This RFA is a one-time solicitation. Generally, future unsolicited competing renewal applications will compete as research project applications with all other investigator-initiated applications and be reviewed by a standing Division of Research Grants study section. However, should the NCI determine that there is a sufficient continuing program need, NCI may announce a request for renewal applications.

Approximately $750,000 in total costs per year for five (5) years will be committed to specifically fund applications which are submitted in response to this RFA. This funding level is dependent on the receipt of a sufficient number of applications of high scientific merit. The total project period for applications submitted in response to the present RFA should not exceed five (5) years. The earliest feasible start date for the initial awards will be July 1, 1990. Although this program is provided for in the financial plans of the National Cancer Institute (NCI), the award of grants pursuant to this RFA is also contingent upon the availability of funds for this purpose. Non-profit and for-profit, and foreign as well as domestic, institutions are eligible to apply.

INQUIRIES

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

Dr. Carl E. Smith
Program Director
Biological and Chemical Prevention
Chemical and Physical Carcinogenesis Branch
Division of Cancer Etiology
National Cancer Institute
Executive Plaza North, Room 700
Bethesda, Maryland 20892
Telephone: (301) 496-4141

Written or telephone inquires concerning the objectives and scope of this RFA or inquires about whether or not specific proposed research would be responsive are encouraged and should be directed to Dr. Carl E. Smith at the above address. The program director welcomes the opportunity to clarify any issues or questions from potential applicants.

POPULATION RESEARCH CENTERS

RFA AVAILABLE: 89-HD-05

P.T. 34; K.W. 0404000, 0730010, 0413002, 0413001, 0715008, 0715182

National Institute of Child Health and Human Development

Application Receipt Date: August 1, 1990

BACKGROUND INFORMATION

The Demographic and Behavioral Sciences Branch (DBSB), Center for Population Research (CPR), National Institute of Child Health and Human Development (NICHD) supports research on population dynamics using a variety of approaches found in the social and behavioral sciences. Population Research Centers are designed to provide core services and facilities to augment the active research grant portfolio at various U.S. universities and research institutions. This Request for Applications (RFA) invites applications for Population Research Centers.

At present, DBSB supports a fixed number of centers which are given a commitment of five years of support that is renewable at five year intervals. There will be three center core grants available in FY91 and this RFA invites competition for these grants, either as new or competing renewal awards.

RESEARCH GOALS AND SCOPE

Center grant applications request support for core services and facilities supporting research grants which can involve any aspect of research supported by DBSB, including research on: fertility, family planning, migration, morbidity and mortality, family and household demography, population modelling, population distribution, population characteristics and composition, sexually transmitted diseases, and AIDS. A grant for a population research center must be predicated on the existence of a substantial number of research grants which will be active on July 1, 1991, and which contain at least one NIH and two other federally funded grants. These grants must be active users of the core facilities and services proposed in the center grant application. Because population research center grants are complex entities, interested applicants should contact DBSB staff for a personal consultation regarding the centers program.

MECHANISM OF SUPPORT

The support mechanism for this program is the P30 Center Core Grant. Up to three awards are anticipated for this RFA. Although this solicitation is included in the plans for FY91, the support of center grants are contingent upon the receipt of funds for this purpose. The applications should be consistent with the guidelines contained in P30 CENTER CORE GRANT GUIDELINES which are available from DBSB. The current policies and requirements that govern the research grant programs of NIH will prevail (Code of Federal Regulations, Title 42, Part 52 and Title 45, Part 74).

METHOD OF APPLYING, REVIEW PROCEDURES AND CRITERIA

Interested applicants should contact DBSB for a personal consultation regarding center grants and to obtain a copy of P30 CENTER CORE GRANT GUIDELINES. Applicants who intend to apply should send a letter of intent outlining the organizational structure of the center and listing the relevant research projects. The letter is optional but strongly encouraged. The letter of intent should be received by DBSB no later than April 1, 1990, but

applicants are encouraged to send it as soon as they decide to apply for the grant so that DBSB staff can be of maximum assistance in the application process. Grant application forms PHS-398 are used to prepare the application. The PHS-398 is available from most business offices or grants/contracts offices at most institutions and can also be obtained from NIH by calling (301) 496-7441. The title of this announcement POPULATION RESEARCH CENTERS should be indicated on the face page of the application in item #2. The RFA label available in the 10/88 version of PHS form 398 must be affixed to the bottom of the face page. Applications must be submitted by August 1, 1990. Send or deliver the original, completed, signed application and four (4) complete copies to:

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

It is extremely important that two (2) additional copies of the application be sent under separate cover to:

Laurence S. Johnston, Ph.D.
Deputy Director, Scientific Review Program
National Institute of Child Health and Human Development
Executive Plaza North, Room 520
6130 Executive Boulevard
Bethesda, Maryland 20892

Late applications will not be accepted.

The applications will be reviewed by the Population Research Committee of the NICHD for scientific merit and the Institutes' Advisory Council for program relevance and policy issues before awards for meritorious applications are made. Review procedures and criteria are detailed in P30 CORE CENTER GRANT GUIDELINES, which is available from DBSB staff. Applications may be subjected to a triage by a peer-review group to determine their scientific merit relative to the other applications received in response to this RFA. NIH will withdraw from competition those applications judged to be noncompetitive and notify the applicant and institutional business official. Those applications judged to be competitive will be further evaluated in the manner stated above. Inquiries regarding this announcement may be directed to:

Regarding scientific matters:

V. Jeffery Evans, Ph.D.
JD, DBSB, CPR
National Institute of Child Health and Human Development
Executive Plaza North, Room 611
6130 Executive Boulevard
Bethesda, Maryland 20892
Telephone: (301) 496-1174

Regarding administrative policy:

Donald Eiler
OGC
National Institute of Child Health and Human Development
Executive Plaza North, Room 501
6130 Executive Boulevard
Bethesda, Maryland 20892
Telephone: (301) 496-5001

TIMETABLE

Application Receipt Date	August 1, 1990
Initial Review Date	March 1991
Review by Advisory Council	June 1991
Anticipated Award Date	July 1, 1991

These programs are described in the catalog of Federal Domestic Assistance No 13.864, Population Research. Awards will be made under the Public Health Service Act, Title III, sec 301 (PL 78-410, as amended; 42 USC 241 and 42 USC 289) and be subject to PHS Grant Policies and Federal Regulations 42 CFR Part 52 and Part 66 and 45 CFR Part 74. This program is not subject the intergovernmental review requirements of Executive Order No. 12372 or to Health Systems Agency Review.

CHOLESTEROL NUCLEATION IN HUMAN GALLBLADDER STONE DISEASE

P.T. 34; K.W. 0705025, 0715085, 1002004, 1002034, 1003016

National Institute of Diabetes and Digestive and Kidney Diseases

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

I. INTRODUCTION

Approximately 25 million Americans have gallstones, and 600,000 cholecystectomies are performed annually in the United States at an estimated cost of 7.5 billion dollars. Although surgical removal of the gallbladder continues to be the predominant, safe and effective way of treating gallstone disease, non-surgical approaches can be very important in certain patients, such as those at high surgical risk. Newer non-surgical techniques for removing cholesterol gallstones have been evolving. These techniques include medical dissolution with bile acids, direct dissolution with infused solvents, and extracorporeal shockwave lithotripsy. These non-surgical approaches leave the gallbladder intact and, therefore, allow gallstones to recur because the basic physiological disorder leading to stone formation has not been corrected. Gallstone recurrence may be as great as 10 percent per year after medical dissolution, with a plateau at about 50 percent after 5 years. The factors that cause recurrence in one-half of the population, and the factors that prevent recurrence in the other half of the treated population need to be elucidated to devise physiologic or pharmacologic methods to prevent gallstone recurrence. Otherwise, the cost and time advantages of the new techniques will be counterproductive because they will merely delay definitive surgical therapy and produce an older population in whom cholecystectomy may need to be performed at greater cost and risk. In addition, by comparing bile and biliary factors in a gallstone-prone population with those in a normal population, the essential features that differ in the two populations can be assessed.

The Division of Digestive Diseases and Nutrition of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) held a workshop in April 1989, on the current state of knowledge of pro- and anti-nucleating factors in the bile; the physical state(s) in which lipids are secreted into the bile and modified in their passage to and through the gallbladder; and the stages through which cholesterol passes in the nucleation process. The major sessions of this workshop dealt with: (1) equilibrium behavior of model lipid systems; (2) phosphatidylcholine vesicles; (3) phosphatidylcholine-cholesterol vesicle model systems; (4) separation and quantitation of cholesterol carriers in native bile; (5) biliary lipids, hepatic secretion and alteration in bile; and (6) nucleating and anti-nucleating agents in native bile and their mode of action. A copy of the papers presented at this meeting is available to interested applicants to this announcement. The proceedings of this conference will be published in August 1990.

II. RESEARCH GOALS AND SCOPE

This Program Announcement is an attempt to bring to the attention of the research community some of the research needs identified at the April 1989 conference on cholesterol nucleation. Topics of research applications of interest include but are not limited to the following examples.

(1) What are the primary cholesterol carriers in bile (micelles, unilamellar vesicles, multilamellar vesicles) and how can they best be quantitated and assessed in human bile without the artifacts created by the spontaneous transfer of lipids among the carriers?

(2) What is the initial step in cholesterol nucleation; is it fusion of lipid vesicles, aggregation followed by fusion, etc.? Is the distribution of cholesterol homogeneous in lipid vesicles or are there patches of high cholesterol content from which the initial step of nucleation occurs? Can crystal formation occur from free monomers?

(3) What is the cellular physiology by which cholesterol, lecithin and bile acids are secreted by the hepatocyte? Where do the vesicles form? Is cholesterol secreted as vesicles? Where are the bile acids added?

(4) How do the putative nucleating or anti-nucleating proteins act? Are they involved in controlling vesicle fusion? Are there other fusogens such as calcium, mucus, bilirubin involved in the initial nucleation step?

(5) What methods can best measure the kinetics of nucleation, since observation of crystal formation is crude, non-quantitative and does not measure the initial step?

(6) How do the lipids change (the kinetics of the system) as they pass from the form in which they are secreted at the canaliculus until they reach the gallbladder? What kinetic changes occur to the mixed micelles that exist in the gallbladder as bile is concentrated and as the gallbladder contracts?

(7) How do the cholesterol crystals grow? Does transfer of molecular cholesterol occur from vesicles to crystals, from micelles to crystals, etc.?

(8) Does lipid transfer occur through a monomeric phase by diffusion or via collision?

(9) What are the best and most practical ways of obtaining bile for study? Can bile be collected as it exits from the Sphincter of Oddi in useable quantity and in a condition that adequately reflects physiologic conditions of mature bile?

(10) Can an oriented liver cell culture be developed that would allow for the study of vesicular secretion and sampling of bile from the canaliculus?

(11) Does medical treatment of gallstones affect nucleation? How is cholesterol removed from crystals and stones during bile acid treatment and are there ways to speed the process?

(12) What are the pro- and anti-nucleators and how do they function? Are they quantitatively and/or qualitatively different in individuals whose gallstones recur versus those who do not reform gallstones?

III. MECHANISM OF SUPPORT

The mechanisms of support for this activity will be the individual research grant (R01), the FIRST Award (R29), and the Program Project (P01). There are no set-aside funds for funding these applications. Applications compete on the basis of scientific merit with all other applications. The review criteria are the traditional considerations underlying scientific merit. The Initial Review Group to which the application is assigned will depend on its scientific content.

IV. APPLICATION AND REVIEW PROCEDURES

A. Deadline

Applications will be accepted in accordance with the usual receipt dates for new research grant applications; i.e. February 1, June 1, and October 1. The earliest possible award dates are approximately nine months after the respective receipt date.

B. Method of Application and Review

Applications will be received and referred to an appropriate study section for scientific merit review by the Division of Research Grants of the NIH. When submitting an application, the principal investigator/program director may suggest an initial review group to which it could be appropriately assigned. However, do not send such correspondence under separate cover; attach it to the application at the time of submission. Although these suggestions will be taken into consideration, the final determination will be made by the PHS.

Applications should be submitted on form PHS-398 (revised 10/88) which is available in the business or grants and contract offices at most academic and research institutions or from the NIH. IMPORTANT: TO IDENTIFY THE APPLICATION AS A RESPONSE TO THIS ANNOUNCEMENT, CHECK "YES" IN ITEM 2 ON THE FACE PAGE OF THE APPLICATION AND ENTER THE TITLE "CHOLESTEROL NUCLEATION IN HUMAN GALLBLADDER DISEASE."

The original and six (6) copies of the application should be mailed to:

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

Inquiries related to the Program Announcement should be directed to:

Sarah C. Kalser, Ph.D.
Program Director, Liver and Biliary Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
Westwood Building, Room 3A-17
5333 Westbard Avenue
Bethesda, Maryland 20892
Telephone: (301) 496-7858

STRUCTURAL BIOLOGY AS APPLIED TO THE PROBLEM OF TARGETED DRUG DESIGN FOR THE TREATMENT OF AIDS

P.T. 34; K.W. 0715008, 0755025, 1003001, 0710030, 1002045

National Institute of General Medical Sciences

BACKGROUND

The National Institutes of Health (NIH) announces its interest in receiving applications to apply modern techniques of molecular structure determination and analysis for the purpose of developing antiviral drugs in the treatment of the Acquired Immunodeficiency Syndrome (AIDS). The central disciplines involved are in the area of structural biology, particularly X-ray crystallography, NMR, and theoretical chemistry as related to molecular modeling. To be effective these must be aided, and to some degree guided, by modern research in molecular biology and pharmacology.

Because of the increased availability of materials and the continued urgency to find a way to combat AIDS, the NIH is re-opening the competition for additional awards to multidisciplinary teams interested in developing approaches to targeted drug design as specifically applied to the human immunodeficiency virus (HIV).

RESEARCH GOALS

- To stimulate the organization of a multidisciplinary research group centered around studies related to structural biology in order to develop approaches to targeted drug design.
- To carry out studies of the structure of the AIDS virus, viral proteins, and other molecules of importance to the understanding of the pathogenesis of AIDS.
- To provide an environment for research training of both graduate students and postdoctoral scientists to think creatively about the problems of targeted drug design.

ELIGIBILITY FOR AWARD

We recognize that the area of targeted drug design is still in its early stage. Therefore, the intent is to provide support for groups which will help in defining the paradigms for future work in this field. However, it is anticipated that the applicant groups will be able to demonstrate the capability of working with specific AIDS-related materials, whether obtained from viral particles or derived by recombinant technologies.

We anticipate that the applicant groups will have particular strengths in several areas, including, but not limited to, X-ray crystallography, molecular modeling, drug design and synthesis, and virology. It should be stressed that these are not requirements, but only the most likely areas that might be encompassed by a proposed program. Other constellations of talent may be effective in achieving the goal of using a knowledge of molecular structure and function to develop materials for the treatment of AIDS. Proposals involving more than one organization, including industrial groups, will be considered as long as an appropriate level of collaboration and interaction can be demonstrated.

Given the emerging nature of this field, a track record of accomplishment in the specific area of targeted drug design is not required, although obviously welcome. Further, it is the intent of this announcement to stimulate the interest of highly qualified investigators in the appropriate disciplines to conduct work in this field. It is expected that the applicants will be able to demonstrate the availability of appropriate materials for study.

REVIEW CRITERIA

- Quality and originality of the proposed research projects, and qualifications of the individual project leaders;
- Involvement of students and more senior investigators both of whom will receive training by participating in the research projects;
- Involvement of investigators having expertise in the appropriate scientific disciplines to provide the breadth needed for an integrated program;
- Evidence of collaboration and interaction among all the groups named in the application; and
- Experience and competence of the Principal Investigator in directing and overseeing a broad program of the type proposed.

SUPPORT MECHANISM

The mechanism of support will be the program project grant. It is expected that three or more investigators, all pursuing independent but interrelated projects, will be involved. One scientist should be designated by the applicant institution as principal investigator and must bear the responsibility for the scientific and fiscal management of the program project grant. Most of the collaborating scientists should be independent investigators. For example, the support of one senior investigator and several postdoctoral and research associate-level scientists is not appropriate as a program project application. However, graduate students and postdoctoral scientists should be included on the individual projects in order to provide training opportunities. Equipment and other core resources necessary for the accomplishment of the objectives of the program project grant may be requested.

Informal interaction and exchange of information between all the groups in the program is expected. All awardees are expected to participate in a yearly conference.

METHOD OF APPLICATION

Use the standard research Grant Application Form PHS-398 (Rev. 10/88). For purpose of identification and processing, the words "STRUCTURAL BIOLOGY AS APPLIED TO THE PROBLEM OF TARGETED DRUG DESIGN FOR THE TREATMENT OF AIDS" should be typed in item 2 of the face page of the application. The receipt dates are January 2, May 1 and September 1. The original and 24 copies should be sent to:

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

ORGANIZATION OF APPLICATION

An introductory section should include: a face page; a description of the objectives of the program as a whole; a list of participating personnel; the consolidated budget for the program project grant (summarizing sub-budgets for the component parts and core); a description of facilities available, including major instruments and special program resources; administrative arrangements for overall scientific leadership, quality control, and management of the program project grant; and a separate, overall listing of proposed percent of effort on the program project grant as well as actual and pending research support and the funding level from all sources for each participating investigator (including percent effort devoted to each project).

Each component of the program project grant proposal should represent an independent research effort as well as demonstrate a relationship to the other components. Each project should be prepared in the format of an individual research grant application, including budget pages, biographical information, outline of the research to be conducted, and separate human and/or animal experimentation certification, if applicable. If support of core resources is requested, a separate section for this should be included.

Interested applicants are encouraged to contact:

Marvin Cassman, Ph.D.
Director, Biophysics and
Physiological Sciences Program
National Institute of General Medical Sciences
Westwood Building, Room 907
Telephone: (301) 496-7463

PSYCHOTHERAPY AND COUNSELING IN DRUG ABUSE TREATMENT

P.T. 34; K.W. 0745060, 0404009, 0404000, 0755015

National Institute on Drug Abuse

Purpose:

The purpose of this announcement is to encourage the study of psychotherapy, behavior therapy, drug abuse counseling, and other non-pharmacological interventions in the treatment of drug abuse. Studies should involve the use of controlled clinical trials or other scientifically/ established research methods. A secondary aim is to encourage the development of instruments to measure the process and outcome of psychotherapy/counseling of drug abusers, and instruments that may be useful in determining therapist and patient characteristics predictive of treatment outcome. Although in the past most drug abuse treatment research has focused on opiate and cocaine abuse, this announcement is intended to encourage the investigation of the treatment of individuals who abuse other types of drugs as well as including polydrug abusers.

Statutory authorities for this grant announcement are sections 301 and 515 of the Public Health Service Act (42 USC 241 and 290cc).

Applicants interested in alcoholism treatment issues are referred to the National Institute on Alcohol Abuse and Alcoholism announcements (1) Matching Clients to Treatment, April 1989, and (2) Development Grants for Alcoholism Treatment Assessment Research, April 1988.

Background:

While drug abuse treatment takes a variety of forms, psychotherapy or drug abuse counseling occurs in virtually every type of drug abuse treatment. According to the 1982 data from the National Drug and Alcoholism Treatment Utilization Survey (NDATUS) report, individual therapy and/or counseling is provided in about 99 percent of drug free, 97 percent of detoxification, 99 percent of methadone maintenance, and 99 percent of multiple modality drug abuse treatment units in this country.

Despite the fact that drug abuse counseling is ubiquitous in drug abuse treatment, surprisingly little is known about it. Additional research is needed to answer a number of questions in this field.

Specific Areas of Interest:

Development of Instruments and Methods in Psychotherapy/ Counseling Research with Drug Abusers -- Psychotherapy research with drug abusers is in an early stage of development. Investigators are encouraged to develop new instruments and refine existing instruments from the mental health field that can be used in controlled psychotherapy/counseling research studies with drug abusers. The development of valid and reliable instruments that measure various aspects of the process and strategies of psychotherapy/counseling, the immediate goals and outcome of these treatments, therapist characteristics predictive of treatment outcome, and patient characteristics predictive of outcome is encouraged.

Analysis of Drug Abuse Counseling/Psychotherapy -- Research is needed to determine how immediate treatment goals are related to long-term treatment goals (i.e., how success in achieving goals within treatment is related to success in achieving goals that result from treatment). For example, investigators may wish to establish different measures of immediate treatment goals, evaluate clients on success in achieving those goals, and then relate success in attaining immediate treatment goals to outcome measures of drug use or social adjustment. Research is also needed to identify, operationally define, and compare the efficacy of different strategies for attaining immediate treatment goals. For example, investigators may wish to establish two distinctive procedures for achieving stress management (or employment) by clients and then compare the efficacy of the two procedures in terms of stress

management. Controlled clinical trials or other rigorous research methods should be used.

Research on Therapist and Patient Variables in Psychotherapy and Counseling -- Studies are sought that assess therapist and/or counselor characteristics and relate these characteristics to effective treatment. Studies that examine the interaction of therapist/counselor and patient variables as related to outcome are also encouraged. Additionally, studies that link the characteristics of patients with successful psychotherapeutic or drug abuse counseling treatment are desired. Measurements of therapist and patient characteristics should be obtained using psychometrically sound instruments. These studies should control for the type of treatment offered and should use an objective, empirical measure of the treatment process that occurs.

Comparative Studies of Different Forms of Psychotherapy of Counseling with Drug Abusers -- Studies that compare the efficacy of individual group, or family psychotherapy with that of drug abuse counseling in patients with and without a dual diagnosis are strongly encouraged. Investigations that compare one form of psychotherapy to another are also needed. Studies that compare the efficacy of behavior therapy to counseling, psychotherapy, or to a combination of behavior therapy and counseling, psychotherapy, or to a combination of behavior therapy and counseling or psychotherapy are also needed. Where effective pharmacotherapies are available, research projects that compare the efficacy of psychotherapy, pharmacotherapy, and the combination of psychotherapy and pharmacotherapy are encouraged.

Studies are also sought that examine the effect of therapist/ patient characteristics across several types of psychotherapy or counseling approaches to assess the relative contribution of therapist, patient, and type of treatment to treatment outcome.

Eligibility:

Applications may be submitted by public or private non-profit or for-profit organizations such as universities, colleges, hospitals, laboratories, units of State or local governments, and eligible agencies of the Federal government. Women and minority investigators are encouraged to apply. Applications are especially encouraged from State governments with research units and/or State governments collaborating with university-based research units.

Application Process:

State and local government agencies may use form PHS 5161-1 (rev. 11/88). All other applicants should use the research grant application from PHS 398 (rev. 10/88). The title of this announcement "PSYCHOTHERAPY AND COUNSELING IN DRUG ABUSE TREATMENT" should be typed in item number 2 on the face page of the PHS 398 application form or in item 9 on the PHS 5161-1.

Application kits containing the necessary forms and instructions may be obtained from business offices or offices of sponsored research at most universities, colleges, medical schools, and other major research facilities. If such a source is not available, the following office may be contacted for the necessary application material:

Grants Management Branch
National Institute on Drug Abuse
Parklawn Building, Room 10-25
5600 Fishers Lane
Rockville, Maryland 20857

Application Receipt and Review Schedule:

Applications received under this announcement will be assigned to an initial review group (IRG) in accordance with established PHS Referral Guidelines. The IRGs, consisting primarily of non-Federal scientific and technical experts, will review the applications for scientific and technical merit. Notification of the review recommendations will be sent to the applicant after the initial review.

Applications will receive a second-level review by an appropriate National Advisory Council whose review may be based on policy as well as scientific merit considerations. Only applications recommended for approval by a Council may be considered for funding.

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

and are not subject to Health Systems Agency review. The review schedule is as indicated below:

Receipt of Applications	Initial Review	Advisory Council Review	Earliest Start Date
February 1	June/July	Sept/Oct	December 1
June 1	Oct/Nov	Jan/Feb	April 1
October 1	Feb/March	May/June	July 1

Review Criteria:

Criteria for scientific/technical merit review of regular research grant applications will include the following: significance and originality from a scientific and technical standpoint of the goals of the proposed research; adequacy of the methodology proposed to carry out the research; qualifications of the Principal Investigator and other key research personnel; availability of adequate facilities, other resources, and collaborative arrangements necessary for the research, appropriateness of budget estimates for the proposed research activities, and adequacy of provisions for the protection of human subjects and welfare of animals subjects as applicable. Criteria for other support mechanisms are contained in separate program announcements available from National Institute on Drug Abuse (NIDA) staff.

Terms and Conditions of Support

Grant funds may be used for expenses clearly related and necessary to conduct research projects, including both direct costs identified with the project and allowable indirect costs of the institution. Funds may not be used to establish, add a component to, or operate a treatment, rehabilitation, or prevention intervention service program. Support for research-related treatment, rehabilitation, or prevention services and programs may be requested only for costs required by the research. These costs must be justified in terms of research objectives, methods, and designs which promise to yield generalizable knowledge and/or make a significant contribution to theoretical concepts.

Grants must be administered in accordance with the PHS Grants Policy Statement (Rev. January 1, 1987) which is available for $4.50 from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402. When ordering copies, the GPO Stock number, GPO 017-020-00092-7, should be referenced.

Further Information:

Further information and consultation on program requirements relevant to psychotherapy research inquiries can be obtained from:

Dr. Lisa Onken
National Institute on Drug Abuse
Parklawn Building, Room 10A-30
5600 Fishers Lane
Rockville, Maryland 20857
Telephone: (301) 443-4060

This program is described in the catalog of Federal Domestic Assistance No. 13.279. Grants will be awarded under the authority of Section 301 of the Public Health Service Act, as amended (42 USC 241) and administered in accordance with the PHS Grants Policy Statement and Federal regulations at 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

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

5333 Westbard Avenue
Bethesda, Maryland 20816

 *U.S. GOVERNMENT PRINTING OFFICE:1989-241-215:00012