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. 17, No. 8
March 4, 1988

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NOTICES

DATED ANNOUNCEMENTS (RFPs AND RFAs)

ONGOING PROGRAM ANNOUNCEMENTS

Presolicitation for: AIDS INFRASTRUCTURE PROJECTS

P.T. 36; K.W. 0780000, 0735000

Division of Research Resources

The purpose of this announcement is to alert the scientific community to a proposed new program designed to enhance the nation's capabilities for AIDS and AIDS-related research.

The Division of Research Resources plans to initiate a program of AIDS infrastructure improvements. Grants would be made to non-Federal domestic institutions ". . . for the repair, renovation, modernization and expansion of existing facilities and the purchase of associated equipment" (House of Representatives Report 100-498, Conference Report to accompany H.J. Res. 395, page 278). Program guidelines are now being developed. Every effort will be made to award these grants as rapidly as possible. All awards will be made competitively.

The terms "repair," "renovation" and "modernization" are governed by the PHS Grants Administration policies for alterations and renovations. The term "expansion" means addition of new usable square footage to an existing building (the additional space could not exceed the building's current net usable square footage). Expansions proposed would be subject to the PHS Grants Administration policies relating to construction. Funds could not be used for the construction of wholly new facilities. Equipment and scientific instrumentation associated with these infrastructure improvements may also be requested.

To be eligible to apply for these awards, an institution must generally have at least one active or pending PHS peer-reviewed AIDS or AIDS-related research award.

It is anticipated that these awards will be in the range of $250,000 to $1,000,000. No indirect costs would be paid. If the total cost of the project exceeds $1,000,000, the applicant must provide assurance that the additional funds are available.

Program guidelines and the Request for Applications will be available on or about May 15, 1988. Receipt date for applications will probably be July 15, 1988; awards are planned for December 1, 1988. The number assigned to this RFA is 88-RR-02.

To receive a copy of the program guidelines or RFA when available, please send two self-addressed mailing labels to the address below. For further information contact:

Mr. C. Alan Moore
Division of Research Resources
Building 31, Room 5B23
Bethesda, Maryland 20892
Telephone: (301) 496-0804

NOTIFICATION OF GRANT APPLICATION RECEIPT AND REFERRAL

P.T. 34; K.W. 1014002

Public Health Service
Alcohol, Drug Abuse and Mental Health Administration
National Institutes of Health

The instructions to the "Application for Public Health Service Grant," Form PHS 398 (revised 9/86), state on page 11 that "the PHS will send the principal investigator/program director and the applicant organization the application's number and the name, address, and telephone number of the executive secretary of the initial review group to which it has been assigned." The purpose of this NIH Guide notice is to inform applicants and organizations that the Division of Research Grants, NIH, will use the address appearing in item 3e. of the face page of the application to send this information to the principal investigator/program director. Item 15., "Official in Business Office to be Notified if an Award is Made," will be used to advise the applicant organization. Therefore, those applicant organizations which prefer a locus other than the business office may designate in item 15 whatever institutional office should receive information regarding application status and Notices of Grant Award.

NOTICE OF TRIAGE

P.T. 34; K.W. 1014002

National Institute of Allergy and Infectious Diseases

The NIAID announces its intent to perform triage in the review of applications relevant to two recently announced Requests for Applications (RFAs). These RFAs are:

RFA 88-AI-01, Programs of Excellence for Basic Research on AIDS, and RFA 87-AI-24, National Cooperative Drug Discovery Groups for the Treatment of Acquired Immune Deficiency Syndrome (AIDS).

These RFAs were published in the October 16, 1987, and September 25, 1987, issues, respectively, of the NIH Guide for Grants and Contracts.

Applications which are incomplete for review or are nonresponsive to the RFA will be screened out and returned to the applicants without further consideration. For each RFA, NIAID will convene a peer review group to perform triage on the complete and responsive applications. The triage group will determine the scientific merit of each application relative to the other applications received in response to the RFA. The NIH will withdraw from competition those applications judged by the peer group to be noncompetitive, and will notify the applicant and the institutional official. Those applications judged to be competitive will be further evaluated for scientific and technical merit by scientific review committees especially convened for this purpose.

DATED ANNOUNCEMENTS (RFPs AND RFAs)

DEVELOPMENT OF MUTAGENESIS ASSAY USING TRANSGENIC MICE

RFP AVAILABLE: NIH-ES-88-11

P.T. 34; K.W. 1002028, 0755010

National Institute of Environmental Health Sciences

The objective of this project is to develop and evaluate one or more *in vivo* mutagenesis assay systems to detect and quantitate gene mutations at a precisely defined target sequence in a mouse exposed to a test chemical.

This project consists of three phases. During Phase I the contractor shall construct and evaluate one or more suitable recombinant DNA vectors containing an appropriate mutagenesis target. The contractor may utilize vectors, mutagenesis target constructs or transgenic mouse strains described in the scientific literature and available to the scientific community. Phase II is concerned with the construction and characterization of transgenic animals and consists of Tasks I and II. During Task I the contractor shall integrate a vector carrying a mutagenesis target into the genome of a mouse embryo and recover a mouse strain or strains transmitting the vector in a Mendelian or sex-linked manner. During Task II, the contractor shall characterize genetically a vector(s) carrying a mutagenesis target. Phase III of the project is concerned with experimentally determining the potential of strains produced in Phase II for use in mutagenesis assays and consists of Tasks I and II. During Task I the contractor shall determine the level of the background mutant frequency of the inserted mutagenesis target in various tissues and organs of the transgenic mice. During Task II the contractor shall determine the utility of the mutagenesis assay by measuring the induced mutant frequency of the inserted mutagenesis target in various tissues and organs after treatment with model mutagens.

The contract will cover a five-year performance period. The Government estimates that the project will require approximately 1.25 professional person years and 2 technical person years of effort each contract year.

This is an announcement of an anticipated request for proposals.

RFP NIH-ES-88-11 will be issued on or about April 1, 1988 with a closing date for receipt of proposals of June 1, 1988.

Requests should reference RFP NIH-ES-88-11 and should be forwarded to:

National Institute of Environmental Health Sciences
Contracts Management Office, OAM
ATTN: Mary B. Armstead, Contracting Officer
79 T.W. Alexander Drive, 4401 Building
P.O. Box 12874
Research Triangle Park, North Carolina 27709

MECHANISMS OF TOBACCO- AND ALCOHOL-RELATED CARCINOGENESIS OF THE ORAL CAVITY

P.T. 34; K.W. 0715035, 0404003, 0404019, 0755030

RFA AVAILABLE: 88-CA-08

National Cancer Institute

Application Receipt Date: May 23, 1988
Letter of Intent Receipt Date: April 8, 1988

The Division of Cancer Prevention and Control (DCPC), National Cancer Institute (NCI), through the Organ Systems Program, announces the availability of a Request for Applications (RFA) on the above subject.

Epidemiologic studies have demonstrated that there are at least two tobacco-related causes of oral cavity cancer: a) snuff-dipping, and b) the combination of chronic alcohol consumption and cigarette smoking. The latter is a major risk factor for squamous cell cancer of the oral cavity. In view of this epidemiologic lead, studies are needed on mechanisms by which alcohol enhances oral cavity cancer induced by tobacco smoke. To test mechanisms proposed, there is a need for development of suitable animal model systems that mimic alcohol enhancement of tobacco-induced squamous cell cancer of the oral cavity, as observed in man. Organ culture or cell culture systems could also prove useful for investigating mechanisms of oral cavity carcinogenesis. The use of smokeless tobacco, especially snuff-dipping, has increased remarkably in the U.S. in recent years particularly among young males; surveys for 1985 indicate that 16 percent of U.S. males between 12 and 25 years of age used smokeless tobacco. Several scientific groups have concluded that snuff-dipping is a cause of oral cancer in humans. Thus, research on the mechanisms of oral cancer induction by local application of snuff or its constituents is likewise necessary and timely.

The objective of this RFA is to invite investigators to use appropriate experimental animal models, organ culture systems, or cell culture systems to elucidate mechanism(s) by which tobacco use may increase the risk for squamous cell cancer of the oral cavity. Studies should focus on mechanisms of induction of oral cancer by (a) snuff-dipping, or (b) the combination of chronic alcohol consumption and tobacco smoking. Appropriate studies could include development of model systems for such studies, as well as research on the mechanisms of oral cancer induction by smokeless tobacco, tobacco smoke, or their carcinogenic constituents. Other novel approaches with appropriate rationales are also encouraged.

Support for this program will be through the traditional NIH investigator-initiated research grant (R01). It is anticipated that approximately five awards, for project periods of up to three years, may be made as a result of this RFA. Applicants are encouraged to submit a letter of intent, and to consult with NCI program staff, before submitting an application.

The RFA label (found in the 9/86 revision of application form PHS 398) 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 of your application such that it will not reach the review committee in time for review.

Copies of the RFA may be obtained by sending a written request to:

Dr. Elizabeth P. Anderson
Organ Systems Program
Division of Cancer Prevention and Control
National Cancer Institute
Blair Building - Room 717
Bethesda, Maryland 20892-4200
Telephone: (301) 427-8818

THE NCI OUTSTANDING INVESTIGATOR GRANT

P.T. 34; K.W. 0715035, 0710039

National Cancer Institute

Application Receipt Date: June 15

SUMMARY AND PURPOSE

The National Cancer Institute (NCI) will continue to accept applications for the Outstanding Investigator Grant (OIG), the purpose of which is to provide long-term support to experienced investigators with outstanding records of research productivity. The OIG is intended to encourage investigators to continue or embark on projects of unusual potential in cancer research. Emphasis will be placed on evidence of recent substantive contributions (i.e., seminal ideas and innovative approaches to resistent problems) and the potential for continued work of high caliber.

Special features of the OIG include: (1) seven year project periods; (2) the delegation of authority to grantee institutions to carry over more than 20 percent of the direct cost authorization of OIGs from one budget period to the next, with the approval of the NCI, and; (3) alleviation of the need to manage more than one grant instrument through consolidation of the OIG principal investigator's (PI's) current cancer-related and peer reviewed support.

ELIGIBILITY

Applications may be submitted only by domestic institutions on behalf of investigators who have recently demonstrated outstanding research productivity for at least five years. There are no age restrictions. Only United States citizens, nationals or permanent residents may be presented as candidates for this grant.

Applications will be accepted by the NCI only when they are cancer related as defined by the Division of Research Grants (DRG) grant referral guidelines. Investigators whose current research support is derived predominantly from sources other than the NCI may not be eligible and are encouraged to discuss their research objectives with appropriate NCI officials before applying.

The OIG PI is required to commit 75 percent of his/her time effort to the OIG project and the institution sponsoring the OIG application is required to commit itself to providing 25 percent of the investigator's support.

Applications which do not meet all of the above eligibility criteria or which have not had approval from the NCI as exceptions to the above criteria will be returned to the applicant.

HOW TO APPLY

- The date of receipt of all OIG applications will be June 15 of each year. They will be processed for review at the earliest possible meeting of the NCAB.

- Application for this award should be made on form PHS 398, revised 9/86 in accordance with instructions in this announce-ment. These applications are available in the business or contracts offices of most academic or research institutions, or from:

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

- The title "NCI OUTSTANDING INVESTIGATOR GRANTS' should be typed in section 2.

- A letter indicating clear and continuing institutional commitment to the applicant must either accompany the application or be received separately before the NCI will begin the initial review process.

INQUIRIES

All potential applicants for this award are advised that the full text of this Program Announcement, containing currently applicable guidelines, is now available and should be requested prior to submitting an application for the June 15, 1988, receipt date.

Please direct inquiries for further information, and requests for copies of the full announcement to:

Mrs. Barbara S. Bynum
Director
Division of Extramural Activities
National Cancer Institute
Building 31, Room 10A03
Bethesda, Maryland 20892
Telephone: (301) 496-5147

ONGOING PROGRAM ANNOUNCEMENTS

DETECTION OF NON-A, NON-B HEPATITIS VIRUS(ES) IN BLOOD

P.T. 34; K.W. 0755010, 0750010, 0715125, 1002045

National Heart, Lung, and Blood Institute

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

The Division of Blood Diseases and Resources (DBDR), National Heart, Lung, and Blood Institute (NHLBI) encourages grant applications on the development of serologic assays to detect non-A,non-B (NANB) hepatitis virus(es) in blood and blood components for transfusion.

Posttransfusion hepatitis remains one of the most serious complications of blood transfusion. The discovery, in 1968, that the viremic phase of serum hepatitis (hepatitis type B, or HBV) could be detected by serologic assay offered hope that virtually all infectious donors would one day be identified and posttransfusion hepatitis prevented. Although the transmission of HBV is almost completely preventable today, it is clear that another virus, namely, NANB hepatitis virus, has supplanted HBV as the major cause of posttransfusion hepatitis. NANB hepatitis virus has not yet been isolated and characterized nor have specific serologic assays been developed to identify the agent(s). There is evidence that more than one agent may cause NANB hepatitis. The diagnosis of NANB hepatitis is presently based on the exclusion, by serologic tests, of known etiologic agents of hepatitis. Serologic studies have shown that the agent of NANB hepatitis is unrelated to hepatitis type A, hepatitis type B, cytomegalovirus, Epstein-Barr virus, varicella-zoster, and herpes simplex.

In the absence of specific serologic tests for the agent, an alternative method for preventing posttransfusion NANB hepatitis is the use of nonspecific, or surrogate, assays. Because of an association with NANB hepatitis, elevated concentrations of alanine aminotransferase (ALT) and the presence of antibody to HBV core antigen in the blood of donors are used as indirect markers for screening for NANB hepatitis virus. The predictive value of these assays in reducing posttransfusion hepatitis, however, is mediocre at best and specific assays to detect the agent of antibody to the agent would be preferable.

This program is described in the Catalog of Federal Domestic Assistance No. 13.839, Blood Diseases and Resources. Awards will be made under the authority of the Public Health Service Act, Section 301 (42 USC 241) and administered under PHS grant policies and Federal regulations, most specifically 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or to Health Systems Agency review.

This solicitation encourages the development of assays to detect antigens, antibodies, or other components directly associated with NANB hepatitis virus in blood and blood components. The tests should be simple to perform, cost-effective, and applicable to the blood bank setting.

Applicants should use the regular research grant application (PHS 398). There are three receipt dates each year for new applications: February 1, June 1, and October 1. If applications are not available at the institution's business office or central application control office, an individual copy may be requested by writing to the Division of Research Grants (DRG), NIH. The original and six copies of the application should be mailed to:

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

All applications will be assigned by the DRG for review according to the NIH process for regular research grant applications. Secondary review will be by the National Heart, Lung, and Blood Advisory Council or other appropriate National Advisory Council. Applications assigned to the National Heart, Lung, and Blood Institute and recommended for approval will compete for available funds with all other approved applications assigned to the NHLBI.

Inquiries should be directed to:

Dr. Luiz H. Barbosa
Blood Resources Branch
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute
Federal Building, Room 504
National Institutes of Health
Bethesda, Maryland 20892
Telephone: (301) 496-1537

ROLE OF GLYCATION IN AGING AND DIABETES

P.T. 34; K.W. 0710010, 0715075, 1003018, 0760005

National Institute on Aging and
National Institute of Diabetes and Digestive and Kidney Diseases

BACKGROUND

Glucose can react nonenzymatically with the amino groups of proteins and nucleic acids to form Schiff bases and a series of other stable covalent adducts (1, 2). This process, referred to as glycation, is part of the Maillard reaction which can not only alter proteins and nucleic acids, but also can lead to cross-linking. Cross-linking of long-lived proteins (e.g. collagen and lens crystallins) increases as a function of age in both animals and man and may be responsible in part for some of the physical changes that occur in aging. One of the most characteristic changes in aging is a progressive stiffness or rigidity of some tissues which may be caused by cross-linking of collagen and elastin (3). Changes in peripheral nerves noted in aging and diabetes could also be mediated by glucose-derived cross-links in the neuronal microtubule protein, tubulin, through inhibition of the guanosine triphosphate-dependent polymerization of nonaggregated tubulin to form microtubles.

Recent research has shown that glycation products which accumulate in long-lived proteins may be removed both by proteolytic turnover, or by the specific uptake and degradation of glycated proteins by macrophages. It is possible that either turnover or macrophagic action decreases with age allowing the accumulation of glycation products in tissue. Glycation of nucleic acids has also been reported. The role of these reactions in aging processes remains to be explored.

Glycation may well be involved in the etiology of a number of age-related diseases. The rigidity of structural proteins due to cross-linking may lead to reduced elasticity in the cardiovascular system resulting in systolic hypertension, decline of cardiac function, renal blood flow, vital lung capacity and oxygen uptake. It has also been noted that low turnover proteins treated with glucose can trap nonglycosylated proteins including albumin, immunoglobulin (e.g. IgG), and low density lipoprotein (LDL). LDL trapping on arterial walls could form the nidus for the formation of atherosclerotic plaque. Increased glycation of osteocalcin with age has also been reported (4), raising the possibility of a role for glycation of this protein in osteoporosis. The proteins present in senile cataracts are reported, to be significantly glycated, which offers a method to monitor and evaluate the effects of glycation in the formation of cataracts.

Chronic hyperglycemia found frequently in diabetes may lead to increased glycation of proteins, including short-lived proteins such as hemoglobin (5) and albumin (6), and glycated proteins may be involved in development of the complications of diabetes, e.g. neuropathy, nephropathy, and macroangiopathy. Thus, diabetes in both animals and humans serves as a model system for the study of glycation.

1. Bunn, H.F., Haney, D.N., Gabbay, K.H. and Gallop, P.M. (1975). Further identification of the nature and linkage of the carbohydrate in hemoglobin AIC. Biochem. Biophys. Res. Commun., 67: 103-109.

2. Koenig, R. J., Blobstein, S. H., and Cerami, A. (1977). Structure of carbohydrate of hemoglobin AIC. J. Biol. Chem., 252: 2992-2997.

3. Monnier, V.M., Kohn, R.R. and Cerami, A. (1984). Accelerated age-related browning of human collagen in diabetes mellitus. Proc. Natl. Acad. Sci. USA, 81: 583-587.

4. Gundberg, C.M., Anderson, M., Dickson, I. and Gallop, P.M. (1986). "Glycated" Osteocalcin in human and bovine bone. The effect of age. J. Biol. Chem., 261: 14557-14561.

5. Bunn, H.F., Gabbay, K.H., and Gallop, P.M. (1978). The glycosylation of hemoglobin: Relevance to diabetes mellitus. Science, 200: 21-27.

6. Guthrow, C.E., Morris, M.A., Day, J.F., Thorpe, S.R. and Baynes, J.W. (1979). Enhanced nonenzymatic glycosylation of human serum albumin in diabetes mellitus. Proc. Natl. Acad. Sci. USA, 76: 4258-4261.

GOALS AND SCOPE

The goal of this announcement is to encourage research on the nonenzymatic glycosylation of macromolecules, especially proteins and nucleic acids, and the role those glycation products play in diabetes and aging processes. This research offers a unique opportunity for interdisciplinary collaboration in the areas of biochemistry, analytical and organic chemistry, immunology, food science and nutrition, epidemiology, cell biology, aging, and diabetes, and the NIA and NIDDK encourage collaborative proposals from clinical and experimental gerontologists, geriatricians, diabetologists, and epidemiologists.

SPECIFIC OBJECTIVES

The NIA and NIDDK seek applications to test hypotheses and elucidate mechanisms including, but not limited to, the following three general areas:

- Structure of glycated products, mechanisms of their systems, and the role of these glycation products in aging, and the long term complications of diabetes.
- The relationships between glycation products and the etiology of age-related diseases, such as cardiovascular disease, cancer, cataracts, arthritis, osteoporosis, etc.
- The relationship between control of diabetes and the reversible and irreversible formation of these glycation products.

Although studies with human cells and tissues are preferred for biological studies, use of other vertebrates may be desirable where shorter life spans and more defined genetic systems are an advantage. Therefore, the NIA supports several colonies of animals and an Aging Cell Repository for use in such research projects. The NIDDK supports a contract for supply of BB rats for use as a model for Type 1 diabetes. Applicants interested in using these resources should contact the following persons:

Contact person for aging rats and mice:
Ms. Jane Soban
Molecular and Cell Biology Branch
Building 31, Room 5C21
National Institute on Aging, NIH
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
Telephone: (609) 966-7377

Contact person for BB diabetic rats:
Dr. Robert E. Silverman
DPB/DEMD/NIDDK
National Institutes of Health
Westwood Building, Room 626
Bethesda, Maryland 20892
Telephone: (301) 496-7888

Contact person for Primates:
Dr. DeWitt Hazzard
Molecular and Cell Biology Branch
Building 31, Room 5C19
National Institute on Aging, NIH
9000 Rockville Pike
Bethesda, Maryland 20892
Telephone: (301) 496-6402

The primary mechanisms for support of this program are:

- Research grant (R01)
- Program Project Award (P01)
- First Award (R29)
- Career grants, which include:
  Special Emphasis Research Career Award (K01) in Nutritional and Metabolic Factors in Aging (NIA only)
  Research Career Development Award (K04)
  Clinical Investigator Award (K08)

REVIEW PROCEDURES

Applications will be reviewed by regular study sections of the NIH, or in the case of P01's and K08's by the review group of the relevant Institute, in accordance with the usual NIH peer review procedures, based on scientific merit. Following study section review, the applications will be evaluated by the appropriate National Advisory Council.

METHOD OF APPLYING

Applications should be submitted on the PHS 398 application form (Rev. 9/86), and will be accepted at regular application deadlines. There are no set-aside funds for funding these applications. If your institution does not have NIH research grant application kits, copies may be obtained by writing:

Office of Grant Inquiries
Division of Research Grants
National Institutes of Health
Westwood Building, Room 240
Bethesda, Maryland 20892
Telephone: (301) 496-7441

Forward the original plus six (6) copies of the completed application to:

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

Potential applicants interested in obtaining further information can call:

Dr. Ann Sorenson
Health Scientist Administrator, Geriatrics Branch
National Institute on Aging
National Institutes of Health
Bethesda, Maryland 20892
Telephone: (301) 496-1033

Dr. Huber R. Warner
Chief, Molecular and Cell Biology Branch
National Institute on Aging
National Institutes of Health
Bethesda, Maryland 20892
Telephone: (301) 496-6402

Dr. Elaine Collier
Assistant Director, Diabetes Research Program
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Westwood Building, Room 622
Bethesda, Maryland 20892
Telephone: (301) 496-7731

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5333 Westbard Avenue
Bethesda, Maryland 20816

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