

NIH Guide for Grants and Contracts

Vol. 12, No . 5, May 20, 1983

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES

IN THIS ISSUE:

Notice

✓ Availability of NIH Extramural Programs
Brochure1

Erratum

✓ Incorrect Telephone Number in Announcement
from the National Library of Medicine,
Vol. 12, No. 4, April 22, 19831

Notice

✓ Reminder to Recipient Institutions
National Research Service Institutional Training Grants2
Index - NATIONAL RESEARCH SERVICE AWARDS

Notice

✓ Notice of Policy Change3
Alcohol, Drug Abuse, and Mental
Health Administration
National Institute on Alcohol Abuse and
Mental Health Administration
Alcohol Research Centers Program
Index - AWARDS

Request for Cooperative Agreements Applications:

✓ RFA NIH-NCI-DCCP-BCB-83-3
Infectious Etiology of Acquired Immune
Deficiency Syndrome (AIDS) and Kaposi's Sarcoma4
National Cancer Institute
National Institute of Allergy and Infectious Diseases
Index - CANCER/ALLERGY

(Continued)

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

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

Have You Moved?

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

Announcement

- Request for Cooperative Agreement Applications: RFA
NIH-NCI-DRCCA-CPB 83-1
The Role of Micro and Macronutrients in
the Prevention of Cancer 10
National Cancer Institute
Index - CANCER

Announcement

- Applications for National Research
Service Award Act 18
National Cancer Institute
Index - CANCER

Announcement

- Cellular Aging Research: Differentiated
Cells in Culture 19
National Institute on Aging
Index - AGING

Notice

- Availability of Updated Guidelines for Competing
Institutional NRSA Applications (T32) to be
Submitted to the National Eye Institute 24
National Eye Institute
Index - EYE

Notice

- Availability of Primary Reference Materials 25
National Heart, Lung, and Blood Institute
Index - HEART, LUNG AND BLOOD

NOTICE

The 1983 edition of NIH Extramural Programs: Funding for Research and Research Training is now available. Limited distribution is being made to all institutions/organizations receiving National Institutes of Health (NIH) awards. Those individuals or institutions wishing to obtain one or more copies may purchase them for \$5.50 each by writing to:

Superintendent of Documents
U.S. Government Printing Office
Washington, D.C. 20402

Please specify GPO Stock No. 017-040-00487-7. Checks should be made payable to the Superintendent of Documents.

ERRATUM

An incorrect telephone number was listed in the following Announcement printed in the NIH Guide for Grants and Contracts, Vol. 12, No. 4, April 22, 1983:

Announcement - Notice of Availability of Request for Training Grant Applications: RFA - RFA-NIH-NLM-EP-83-1 Health Computer Sciences Research Training

National Library of Medicine

At the bottom of page 22 the correct telephone number should be:

(301) 496-4221

NOTICE**REMINDER TO RECIPIENT INSTITUTIONS****NATIONAL RESEARCH SERVICE INSTITUTIONAL TRAINING GRANTS**

PHS policy requires that a Statement of Appointment (PHS Form 2271) be received by the NIH awarding unit before any stipend is paid to a trainee. The actual practice of the submission of these forms has become irregular. It is incumbent upon us all to keep the system accurate, especially in these stringent budgetary times when research training funds are in unusually short supply. Your attention is called to the fact that stipends paid from institutional research training grants prior to the submission of an appointment form may be disallowed.

We ask the assistance of Program Directors and Business officials in the prompt submission of these forms. For this purpose, we restate the policy in this matter as originally published in the NIH Guide for Grants and Contracts Special Edition, Vol. 11, No. 7, June 18, 1982, National Research Service Awards.

"Statement of Appointment (Form PHS 2271)

The Institution must submit this form to the awarding unit at the start of each trainee's appointment or reappointment. No stipend or other allowance may be paid until the appointment form has been submitted along with a signed Payback Agreement. It is important to note that the information on the Statement of Appointment and the Termination Notice is the basis for determination of the length or amount of an individual's payback requirement. The program director and the institutional financial officials should coordinate the information reported on the Statement of Appointment. It should be treated as a financial document for obligating costs (stipends) which later are reflected as part of the total costs in the Financial Status Report."

NOTICE

NOTICE OF POLICY CHANGE

**ALCOHOL, DRUG ABUSE, AND MENTAL HEALTH ADMINISTRATION
NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM
ALCOHOL RESEARCH CENTERS PROGRAM**

February 1983

This notice describes a recent policy change regarding the level of support for National Alcohol Research Centers of the National Institute on Alcohol Abuse and Alcoholism. The changes are applicable to grant awards made under this program and became effective February 1, 1983. This program is authorized under Section 504 of the Comprehensive Alcohol Abuse and Alcoholism Prevention, Treatment, and Rehabilitation Act.

Change in Maximum Level of Support

The maximum annual grant award for the support of a new National Alcohol Research Center will be \$1,000,000, which includes direct and indirect costs, for each year except the initial year. The first year of support will remain at a maximum of \$500,000 including direct and indirect costs. For currently funded Centers, the maximum level of support will be effective after December 1, 1983.

REQUEST FOR COOPERATIVE AGREEMENTS APPLICATIONS: RFA**NIH-NCI-DCCP-BCB-83-3****INFECTIOUS ETIOLOGY OF ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)
AND KAPOSZ'S SARCOMA****NATIONAL CANCER INSTITUTE****NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES**

Application Receipt Date: August 1, 1983

The National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Diseases (NIAID) invite applications for Cooperative Agreements from interested investigators for both basic and applied studies designed to determine the etiology of acquired immune deficiency syndrome (AIDS) and its associated aggressive generalized form of Kaposi's sarcoma. The determination of etiology may make possible the development of appropriate methods for eventual prevention and/or control of the disease.

Cooperative Agreements are awarded to both nonprofit and profit organizations and institutions. This type of solicitation is utilized when it is desired to encourage investigator-initiated research projects in areas of special importance to the NIH and where substantial programmatic involvement by staff is anticipated. Applicants funded under the RFA are supported through cooperative agreements. The RFA solicitation represents a single competition, with a specified deadline for receipt of applications. All applications received in response to the RFA will be reviewed by the same NIH Initial Review Group (IRG) and by the National Cancer Advisory Board and/or the National Advisory Allergy and Infectious Diseases Council. The specific deadline for the receipt of response to the RFA is August 1, 1983. Applications should be prepared and submitted in accordance with the aims and requirements of the following sections:

- I. Background Information
- II. Research Goals and Scope
- III. Mechanism of Support
- IV. Nature of Collaboration with NCI/NIAID Staff:
Terms of Award
- V. Review Procedures and Criteria
- VI. Method of Applying
- VII. Inquiries

This program is described in the Catalog of Federal Domestic Assistance No. 13.393, Cancer Cause and Prevention Research and No. 13.856, Microbiology and Infectious Diseases Research. Awards will be made under the authority of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended; 42 USC 282) and administered under PHS grant policies and Federal Regulation 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to A-95 Clearinghouse or Health Systems Agency review.

I. BACKGROUND INFORMATION

The Division of Cancer Cause and Prevention (DCCP) of the National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Diseases (NIAID) invite applications for Cooperative Agreements to support research projects into the microbiological etiology of Acquired Immune Deficiency Syndrome (AIDS) in humans. This is a new disease which was first reported in 1981 in homosexual males. The syndrome is characterized by severe immunosuppression, an associated outbreak of Kaposi's sarcoma and lymphomas, and/or a variety of opportunistic infections. The immunological status is commonly characterized by lymphopenia, cutaneous anergy, reduced helper T-lymphocyte subpopulations, and inversion of the helper/suppressor T-lymphocyte ratio. In addition, affected individuals may often have a prodrome of chronic fever, weight loss, diarrhea, and lymphadenopathy. Among affected subjects there is frequent evidence of infection with multiple viruses. AIDS patients now include both homosexual and bisexual males, heterosexual intravenous drug users, hemophiliacs, Haitians and some infants. In addition to disorders of immunological function, approximately half of the AIDS victims suffer from Pneumocystis carinii pneumonia and about one-third have Kaposi's sarcoma (KS) or lymphomas. The mortality rate is near forty percent overall, but closer to eighty-five percent for cases diagnosed early in 1981. The long-term prognosis for AIDS is very poor.

The recent involvement of hemophiliacs, apparently normal children, and some common epidemiological features now suggest a blood-borne, venereal, or close-contact transmissible biological agent as the causative factor. Two viruses, human cytomegalovirus (HCMV) and Epstein-Barr virus (EBV), have already been linked with AIDS, KS, and lymphomas. HCMV has been associated with KS by at least one molecularly oriented study of KS tissue, and EBV determined nuclear antigen has been demonstrated in tissues of several AIDS patients with a Burkitt's-like lymphoma. Further, several viruses have already been associated with certain human cancers: the etiological association of EBV with nasopharyngeal carcinoma; the papilloma viruses with malignancies of the skin, cervix and anus; HCMV with KS; and human T-cell leukemia-lymphoma virus (HTLV) with several malignancies. Recent advances in the study of cellular and viral oncogenes relative to cancer induction appear promising in ferreting out a basic mechanism of cancer induction. All these advances indicate that there is a rational basis for initiating systematic efforts to search for the transmissible agent presumed responsible for the AIDS syndrome and Kaposi's sarcoma.

II. RESEARCH GOALS AND SCOPE

A. Scope

The purpose of this RFA is to stimulate studies aimed at a direct microbiological approach to the problem. It is designed to encourage studies on the search for the isolation, and the characterization of the biological agent(s) which may be the primary causative factor(s) in AIDS and KS. The studies proposed should encompass not only the classical microbiological technologies for isolation and characterization of the agent, but also the contemporary technologies of immunology, cytogenetics, and molecular biology. Since HCMV and EBV, both transforming viruses, have been implicated in immune suppression and in association with KS and lymphomas, definitive studies of HCMV and EBV in terms of their relationship to the etiology of AIDS and KS would be considered as pertinent to the objectives of

the RFA. However, it is emphasized that projects involving either or both RNA-core or DNA-core viruses, bacteria, rickettsia, or other potentially causative agents will be considered. Examples of the types of studies that might be appropriate include:

1. Direct in vivo and in vitro efforts at isolation, identification, and characterization of the causative biological agent.
2. Analysis of human tissue with appropriate tests indicative of the presence, state of integration, and location of viral or pro-viral DNA, or other infectious forms.
3. Recognition and identification of marker antigens of pathognomonic significance.
4. Cytogenetic analysis for chromosomal changes that relate to disease induction.
5. In vitro search for direct morphological transformation and/or cytopathology of appropriate target cells.

The NCI/NIAID plan at least annual meetings of collaborating investigators funded under this RFA ("working group"). Collaborating investigators may constitute an independent working group or may become part of an already established AIDS working group. These annual or more frequent meetings of the working group will provide an opportunity for the development of collaborative arrangements between investigators performing complementary research. At this time it is impossible to explicitly outline the nature of such arrangements since the scope of projects to be funded is unknown. Typical arrangements may include the exchange of selected reagents, the exchange of certain human specimens, and/or the exchange of current information. The NCI/NIAID will require these types of exchange and will attempt to facilitate them. This cooperation will hasten the resolution of the important questions relevant to this epidemic and will result in a more effective allocation of funds. It is anticipated that NCI/NIAID staff will play a key role in coordinating and facilitating such collaborations as various research activities evolve by identifying data points, comparing protocols, comparing results, etc. Additional details of this involvement are outlined below under "Terms of Award."

B. Safety

Because of the unknown nature of the disease, investigators will be required to utilize appropriate laboratory control measures. Procedures should be used representative of good microbiological techniques applicable to the handling of materials containing hepatitis B virus or other infectious agents which may be transmitted by ingestion, parenteral inoculation, or exposure of mucous membranes to infectious droplets. As an additional precaution, it may be advisable to use a biological safety cabinet. See also V.C.4. for a reference to recommended procedures and precautions.

III. MECHANISM OF SUPPORT

Awards will be made as Cooperative Agreements. These are assistance relationships involving substantial involvement with NCI/NIAID staff, as outlined under Part IV, "Terms of Award." NCI/NIAID anticipate making multiple awards as a result of this request. Up to \$2,000,000 (\$1,000,000 by NCI and \$1,000,000 by NIAID) will be allocated to fund the initial year's awards for meritorious applications. Awards will be made for project periods of up to five years. All policies and requirements which govern the grant programs of the PHS apply, including the requirement for cost sharing.

IV. NATURE OF INVOLVEMENT OF NCI/NIAID STAFF: TERMS OF AWARD

This section outlines the interactions between recipients of these cooperative agreements and NCI/NIAID program staff.

1. The awardees shall develop research protocols and plans in accord with their individual interests and strengths as well as the minimum requirements included in these terms of award.
2. The NCI/NIAID staff will serve as a resource of information on the activities of various members of the working group and will act to facilitate collaboration among involved researchers. It is in the context of the Working Group meetings that the awardees, with the assistance of NCI/NIAID staff, will identify and develop these collaborative areas. It is anticipated that there will be exchange of selected reagents, exchange of certain human specimens, and/or exchange of current information and that NCI/NIAID staff will facilitate interaction by identifying data points, comparing protocols, and comparing results.

V. REVIEW PROCEDURES AND CRITERIA

A. Assignment of Applications

Applications will be received by the NIH Division of Research Grants (DRG) and referred to the same Initial Review Group for scientific merit review. NIH referral guidelines generally will apply, and DRG will work with both NCI and NIAID for assignment of the grant applications.

B. Review Procedures

All applications submitted in response to this RFA will be reviewed in competition with each other by:

1. An NIH peer review group and
2. The National Cancer Advisory Board and/or the National Advisory Allergy and Infectious Diseases Council

C. Review Criteria

Applications must be responsive to this RFA, in the sense of being directed towards the attainment of the stated programmatic goals (see II. RESEARCH

GOALS AND SCOPE). If the application is judged by the NIH to be unresponsive, it will be returned to the applicant.

The factors considered in evaluating applications in response to this RFA will be:

1. Scientific merit of research approach, design, and methodology.
2. Research experience and competence of the Principal Investigator and staff to conduct the proposed studies.
3. Adequacy of time (effort) which the Principal Investigator and staff would devote to the proposed studies.
4. Adequacy of existing/proposed facilities and resources. This includes adequacy of patient resources to ensure completion of meaningful studies in a reasonable period of time. Additionally, the facilities used for these studies must be suitable to permit appropriate laboratory control measures for agents equivalent to hepatitis B virus. Facilities and laboratory practices must be consistent with the following reference: CDC Morbidity and Mortality Weekly Report, Vol. 31, No. 43, November 5, 1982.
5. Scientific, technical or medical significance and originality of proposed research.
6. Reasonableness of proposed costs.

VI. METHOD OF APPLYING

A. Format of Applications

1. Applications must be submitted on form PHS 398 (Rev. 5/82), the application form for research grants. Application kits are available at most institutional business offices, or may be obtained from the DRG, NIH. The format and detail applicable to regular research grant applications should be followed and the requirements specified under Review Criteria (V.C.) must be fulfilled. Since NCI/NIAID plan at least an annual meeting of the Working Group, applicants are encouraged to include in their budget travel funds for the principal investigator to attend at least one meeting per year in Bethesda, Maryland.
2. The number and title of this RFA should be typed in section 2 on the front page of the grant application form.

B. Application Procedure

1. The completed original application and six (6) exact copies should be sent or delivered to:

Division of Research Grants
National Institutes of Health
Westwood Building - Room 240
5333 Westbard Avenue
Bethesda, Maryland 20205

an additional one (1) copy should be sent to:

Dr. Jack Gruber
Acting Chief
Biological Carcinogenesis Branch, DCCP
National Cancer Institute
National Institutes of Health
Landow Building - Room 9A22
Bethesda, Maryland 20205

Telephone: (301) 496-9740

an additional copy should be sent to:

Dr. William P. Allen
Virology Program Officer
BVB/MIDP
National Institute of Allergy and
Infectious Diseases
Westwood Building - Room 736
Bethesda, Maryland 20205

Telephone: (301) 496-7453

and one copy of the application should also be sent to:

Dr. Harold Waters
Division of Research Grants
National Institutes of Health
Westwood Building - Room 2A16
Bethesda, Maryland 20205

- C. To ensure their review, applications should be received by August 1, 1983. This is a one-time request for applications. NCI/NIAID have no plans to reissue this announcement at any future date. Applications received after the above date will be considered unresponsive and will be returned without review. The DRG will not accept any application in response to this announcement that is the same as one currently being considered by any other NIH awarding unit.

VII. INQUIRIES

Inquiries may be directed to:

Dr. Jack Gruber
Biological Carcinogenesis Branch
National Cancer Institute

or to

Dr. William P. Allen
Bacteriology-Virology Branch
National Institute of Allergy and
Infectious Diseases

at the above addresses.

ANNOUNCEMENT**REQUEST FOR COOPERATIVE AGREEMENT APPLICATIONS: RFA****NIH-NCI-DRCCA-CPB 83-1****THE ROLE OF MICRO AND MACRONUTRIENTS IN THE PREVENTION OF CANCER****NATIONAL CANCER INSTITUTE**

Letter of Intent Receipt Date: July 1, 1983

Application Receipt Date: August 1, 1983

The Division of Resources, Centers, and Community Activities (DRCCA), National Cancer Institute (NCI), invites applications for cooperative agreements to support risk reduction clinical trials which are directed at examining the role of micro and macronutrients in the prevention of cancer.

The proposed studies should seek to elucidate further the protective effects of inhibitors or of dietary prescriptions in reducing the incidence of cancers of specific sites.

Applicants funded under this RFA will be supported through the cooperative agreement mechanism. An assistance relationship will exist between NCI and the awardees to accomplish the purpose of the activity. As more fully described later in this announcement, the recipients will have primary responsibility for the development and performance of the activity. However, there will be government involvement with regard to (1) securing an Investigational New Drug (IND) approval from the Food and Drug Administration (FDA), (2) monitoring of safety and toxicity and, (3) coordination and assistance in obtaining the chemopreventive agent.

This RFA solicitation represents a single competition, with a specified deadline of August 1, 1983, for receipt of applications. All applications received in response to the RFA will be reviewed by the same National Institutes of Health (NIH) Initial Review Group (IRG).

Applications should be prepared and submitted in accordance with the aims and requirements described in the following sections:

This program is described in the Catalog of Federal Domestic Assistance No. 13.393, Cancer Cause and Prevention Research. Awards are under authorization of the Public Health Service Act, Section 301(c) and Section 402 (Public Law 78-410, as amended; 42 USC 241; 42 USC 282) and administered under PHS grant policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to A-95 Clearinghouse or Health Systems Agency review.

I. BACKGROUND

Epidemiologic studies and laboratory research results support the concept that the incidence of cancer may be influenced by the levels of various nutrients and non-nutritive substances in the diet. A number of natural micronutrients including vitamin C, beta carotene, vitamin A or its analogs, selenium and alpha tocopherol have been associated, in animals or test systems, with the inhibition of carcinogenesis or have been associated with reduced cancer incidence, in epidemiological investigations.

The level of dietary fat has shown a positive correlation with incidence of cancer of several sites while increased fiber intakes has shown a negative correlation with the incidence of cancer at several sites. A number of mechanisms have been postulated including increased detoxification of carcinogens, alteration of metabolism by decreased activation, scavenging of the active molecular species, prevention of the carcinogenic agent from reaching the critical target in the cell, altering permeability or transport, and competitive inhibition. Other possible mechanisms include antagonism of promoting agents or induction of differentiation of malignant cells.

Because of the numerous reports concerning the effectiveness of dietary manipulation or the administration of certain compounds in interfering with carcinogenesis in animals and the many epidemiological studies suggesting a possible negative association of certain dietary factors with cancer incidence, clinical intervention studies are now encouraged.

II. OBJECTIVES AND SCOPE

The purpose of this RFA is to solicit applications from qualified investigators interested in developing and implementing randomized controlled clinical trials to study the effect of micro- or macronutrients on cancer risks in humans. Micronutrients include, but are not limited to the following: beta carotene, vitamin A or analogs, vitamin C, selenium and alpha tocopherol. In addition, intervention trials involving several macronutrients including fats, vegetables, fruits, cereals and fibers will be considered.

This RFA is limited to clinical trials but excludes focus on skin cancer as the study end-point with the exception of melanoma.

The studies of interest are risk reduction clinical trials involving (a) normal populations, (b) populations known to be at increased risk but free of neoplasia, or (c) high risk populations with identified precursor or pre-cancerous lesions. These studies would require the administration of the designated inhibitors or dietary prescriptions in a randomized study with follow-up to determine the effects. Proposals involving studies of populations already having neoplastic lesions are not acceptable within the scope of this RFA.

Several items with regard to the proposal itself are provided as follows:

1. The applicant is encouraged, wherever germane, to focus attention on a specific target group, or to identify a source of participants and to

address the methodological, organizational, and theoretical issues in a detailed manner.

2. The applicant should provide a description of the target population or group chosen and should justify the selection of this group. The group should be defined, where appropriate, by age, sex, race, socioeconomic status, dietary customs, education, geographic location, occupational or life style risk factors, and relevancy to a specific cancer problem and to its possible prevention by designated inhibitors or dietary manipulations.
3. The applicant should specify the methods to be used to document nutrient intake at baseline and adherence to the prescribed intervention during the course of the trial.
4. The applicant should clearly indicate the clinical chemistry and biologic aspects of the study to include collection, storage, handling and analysis of biological samples. The methods and equipment to be utilized and the technical qualifications and experience of the personnel involved must be addressed.
5. The applicant should elucidate any known or potential safety or toxicity considerations, the techniques and procedures for monitoring and reporting any adverse health effects and appropriate dose modifications based on toxicity monitoring.
6. The applicant must indicate his agreement to work cooperatively with NCI staff in the implementation and conduct of the study.

III. MECHANISM OF SUPPORT

Awards will be made as Cooperative Agreements. These are assistance relationships involving cooperation with NCI staff, as outlined under Part IV, "Terms of Award." The planning, direction and execution of the proposed research will be the responsibility of the applicant with assistance from the NCI staff. The total project period for applications submitted in response to this RFA should not exceed five years. The intent is to fund projects of high scientific merit, with total costs amounting to \$3 million per year. This level of activity is dependent on the receipt of a sufficient number of applications of high scientific merit. Although this program is provided for in the financial plans of the NCI, the award of grants pursuant to this RFA is also contingent upon the continuing availability of funds for this purpose.

The awardees will develop a proposal based on their past experience, research interests, and information generated through pilot projects. The protocol shall be clearly written, well documented and appropriately annotated for background, objectives, eligibility criteria, treatment administration, statistical considerations and quality control.

A copy of the format which should be followed in the development of the proposal is available from the Program Director, listed in VII.

IV. NATURE OF COLLABORATION AND ASSISTANCE FROM THE NCI STAFF: TERMS OF AWARD

This section outlines the collaboration between recipients and NCI program staff.

A. Safety and Toxicity Review

Safety and toxicity aspects of the peer reviewed, approved, high priority proposals will be reviewed by an NCI staff committee chaired by the Associate Director, Prevention Program, DRCCA, NCI, or his designee. The primary purposes of this review are: (1) to insure that safety and toxicity issues have been addressed, and (2) to assure that the proposed research is in compliance with all FDA requirements and approvals. The NCI staff will follow up on these recommendations to ensure adequate safety and compliance.

B. Quality Control and Adverse Reaction Reporting

1. The awardees are expected to set up mechanisms for quality control. Quality control will require some or all of the following as relevant: compliance with protocol requirements for eligibility, treatment and follow-up; laboratory data; dietary data; pathological materials; and operative reports.
2. For chemopreventive agents, investigators are required to conform to NCI guidelines for use of investigational drugs including investigator registration (Form 1573), maintaining a record of drug receipt and reporting of adverse drug reactions. Life threatening or unexpected toxicity must be reported by the investigator immediately by telephone to NCI and confirmed with details in writing within two weeks. The investigator will be responsible for amending protocols and consent forms based on new toxicity information sent to the investigators by NCI staff. The NCI staff has developed mechanisms for prompt reporting to other investigators of all unexpected or serious toxicity caused by IND agents.
3. NCI staff is responsible for assuring the adequacy of safety monitoring and quality control for all chemopreventive studies involving NCI-sponsored IND drugs. The NCI staff will review the mechanism established by each applicant for quality control of clinical studies. These mechanisms must conform with FDA regulations.

NCI is establishing a clinical chemistry quality assurance program which will provide guidance in the quality control of selected laboratory determinations. Each applicant will be expected to participate in the laboratory quality control activity if applicable.

C. Data Management and Reporting Requirements

1. Data acquisition and analysis is the responsibility of the investigator. Data which must be collected are listed in the protocol format available from the Program Director; see section VII. Investigators will be required to submit reports to NCI using the following schedule and format:

a. Semiannual Reports

Semiannual scientific reports should report on the progress of the project during the previous six months and the cumulative progress of the study.

The semiannual report should include:

- (1) A concise narrative progress summary covering the previous six months (give dates of the six-month period utilized) and the cumulative progress of the study.
- (2) Tabular displays of:
 - (a) Accrual history of the project generally broken down in six-month periods. In addition to total accrual, report number ineligible, number inevaluable, and number of study violations.
 - (b) Interim analyses of results, if appropriate.
 - (c) Toxicities, graded as to severity.
- (3) Provide explanations in case of any of the following: increase or decrease in accrual, any unusual or unexpected incidence of ineligible or inevaluable participants, or any unusual or unexpected study violations.
- (4) Brief descriptions of quality control measures such as review of records, on-site monitoring, biochemical monitoring of study compliance, etc.
- (5) A list of all publications related to work under this cooperative agreement. This listing should include published references, manuscripts in press or submitted. Submit two copies of each reprint.
- (6) Curriculum vitae will be provided if there has been a requested change in any of the project investigators.

b. Annual Report

An annual expenditure report and budget for the forthcoming 12-month period shall be submitted at least two months prior to the funding anniversary using standard NIH formats.

c. Final Study Report

The final report of a completed study shall consist of detailed analyses of results and toxicity, plans for publications, a comprehensive list of all previous publications related to this project, and plans for archiving and storing the study records.

2. The NCI staff will have access to the data for reviewing toxicity and safety, preparing NDA applications and for any monitoring required by other Federal agencies. The data generated, however, is the property of the awardee institution. NCI staff may encourage and facilitate sharing of data between investigators when this is in the mutual interests of the investigators and NCI.

D. Investigational New Drug (IND)

The NCI will have the option to cross file or independently file an IND on investigational drugs evaluated in trials supported under the cooperative agreements.

NCI will advise investigators of specific requirements and changes in requirements concerning investigational drug management for compliance with NCI and the FDA guidelines and regulations. Investigators performing trials under cooperative agreements will be expected, in cooperation with the NCI, to comply with all FDA monitoring and reporting requirements for investigational agents, for reporting adverse reactions, and for maintaining necessary records of drug receipt, use, and distribution.

Approval by the Institutional Review Board (IRB) must be obtained by awardees on all protocols because of the involvement of human subjects.

Informed Consent Forms must comply with NIH guidelines and should include preclinical and clinical toxicology information as relevant.

Awardees will be responsible for amending Informed Consent Forms if new toxicity information becomes available.

V. REVIEW PROCEDURES AND CRITERIA

A. Review Method

Each application submitted in response to the RFA will be reviewed by: (1) an appropriate review panel of the NIH, (2) a DRCCA safety review and (3) the National Cancer Advisory Board at its regularly scheduled quarterly meeting which reviews grants after the initial review.

B. Review Criteria

Applications must be responsive to this RFA, in the sense of being directed towards the attainment of the stated programmatic goals, and fall within one or more of the specified research categories (see II. OBJECTIVES AND SCOPE). If the application is judged by the NCI to be not responsive, the applicant will have the opportunity of having the application considered along with other unsolicited proposals received by the NIH in the review cycle which is current at that time.

The factors considered in evaluating the scientific merit of each response to this RFA will be:

1. Scientific merit of the research approach, design, and methodology to include considerations of toxicity, safety and quality assurance of the research.
2. Scientific, technical, or medical significance and originality of the proposed research.
3. Research experience and/or competence of the Principal Investigator and staff to conduct the proposed studies.
4. Adequacy of time (effort) which the Principal Investigator and staff would devote to the proposed studies.
5. Relevancy and appropriateness of the specific target population along with assurance as to their accessibility.
6. Identity of sources of data, tissues, fluids, etc., procedures for their analysis and assurances as to their accessibility.
7. Accessibility of the inhibitory or other agents. If an IND is held for the agent, that information should be furnished at the time of proposal submission. If the NCI is to assist in obtaining the IND, that information should be furnished.
8. Reasonableness of the proposed budget and duration.

VI. METHOD OF APPLYING

A. Letter of Intent

Prospective applicants are asked to contact program staff by telephone or to submit a one-page letter of intent which includes a very brief synopsis of proposed areas of research and identification of any other participating institutions. This telephone contact or letter of intent should be addressed to Dr. W. Malone at the address located under VII. The Institute requests such contact to provide an indication of the number and the scope of applications to be received and for the purposes of identification of overlap and/or redundancy with currently funded research. The letter of intent is not binding; it will not enter into the review of any proposal subsequently submitted, nor is it a mandatory requirement for the submission of the application.

B. Format of Application

Applications must be submitted on Form PHS 398, the application form for research project grants. Application kits are available at most institutional business offices, or may be obtained from the Division of Research Grants (DRG), NIH. The conventional presentation format and details applicable to regular research grant applications should be followed, and the requirements specified under Review Criteria (see section V.B.) must be fulfilled. The words "PROPOSAL IN RESPONSE TO RFA NIH-NCI-DRCCA STUDIES TO EXAMINE THE ROLE OF MICRO AND MACRONUTRIENTS IN THE PREVENTION OF CANCER," must be typed in section 2 of the face page of the application.

C. Application Procedures

The completed original application and six (6) copies should be sent or delivered to:

Division of Research Grants
National Institutes of Health
Westwood Building - Room 240
5333 Westbard Avenue
Bethesda, Maryland 20205

To ensure their review, applications should be received by August 1, 1983. Applications received after that date will not be considered under this RFA. A copy of the application should also be sent to Dr. Malone at the address shown below.

VII. INQUIRIES

Inquiries may be directed to:

Winfred F. Malone, Ph.D., M.P.H.
Chemoprevention Branch
Blair Building - Room 624
National Cancer Institute
Bethesda, Maryland 20205

Telephone: (301) 427-8648

ANNOUNCEMENT

NATIONAL CANCER INSTITUTE

The National Cancer Institute (NCI) invites applications for National Research Service Award Act research training grants, individual postdoctoral fellowships and senior postdoctoral fellowships in all the basic and applied sciences relevant to cancer. Research training grants may support both predoctoral and postdoctoral trainees. Applications proposing quality research training in the following areas will be of special interest to the NCI.

Surgical Oncology - Postdoctoral research training for physicians in the basic or applied sciences.

Radiation Oncology - Postdoctoral research training for physicians in the basic or applied sciences.

Preventive Oncology - Predoctoral and postdoctoral research training in the following areas:

1. cancer control science;
2. endogenous and exogenous carcinogens;
3. mechanisms of carcinogenesis;
4. genetics of cancer susceptibility and resistance;
5. cancer epidemiology and biostatistics
6. interruption and/or reversal of carcinogenesis;
7. protection from exposure to carcinogens or protection from their effects;
8. chemoprevention;
9. cancer-related nutrition;
10. behavioral sciences as they relate to prevention oncology;
11. immunoprevention;
12. risk factor modification.

Inquiries should be addressed to:

Barney Lepovetsky, Ph.D., J.D.
Chief, Cancer Training Branch
Division of Resources, Centers and
Community Activities
National Cancer Institute
National Institutes of Health
Blair Building - Room 717
Bethesda, Maryland 20205

Telephone: (301) 427-8898

ANNOUNCEMENT

CELLULAR AGING RESEARCH: DIFFERENTIATED CELLS IN CULTURE

NATIONAL INSTITUTE ON AGING

Application Receipt Dates: July 1, November 1, March 1

I. INTRODUCTION

The National Institute on Aging (NIA) was established in 1974, to conduct and support biomedical, behavioral and social research and training related to the aging process and the diseases and other special problems and needs of the aged. Consistent with this mandate, Cellular Biology, a subprogram of the Molecular and Cellular Biology Program, supports research on mechanisms of cellular aging with the use of cell culture technologies. The purpose of this announcement is to encourage further research and training activities in cellular aging utilizing tissue and organ specific cells in culture.

II. BACKGROUND

Cellular events are probably major determinants of longevity and senescence. The study of cells as they "age" in culture and of cells derived from humans and experimental animals of various ages permits investigation of cellular events consequent to aging independent of the complexity of the whole organism. To date most such studies have used fibroblast-like cells of dermal and lung origin, these being easily obtained and cultured. Although such cells have yielded valuable information on various aspects of in vitro cellular aging, and on cellular and molecular biology in general, these systems have not yet been sufficiently characterized with respect to cell heterogeneity in mass cultures, in vivo precursors of in vitro cultures, and specific functional markers that can be compared with those of cells in vivo. The NIA earlier issued an announcement inviting applications addressing these questions (NIH Guide for Grants and Contracts, Vol. 9, No. 2, January 25, 1980).

Because of recent advances in cell-culture technologies, an increasing number of differentiated cells in culture are likely to be available for comparative studies of cellular aging. Recognizing that phenotypic, and perhaps genotypic, differences exist between cells in vitro and in vivo, nonetheless many differentiated cells do express known functional traits when maintained in culture. Several differentiated

This program is described in the Catalog of Federal Domestic Assistance No. 13.866, Aging Research. Awards will be made under the authority of the Public Health Service Act, Title III, Section 301 (Public Law 78-410, as amended; 42 USC 241) and administered under PHS Grant Policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74, and section 472, 42 USC 2891-1, and administered under Federal Regulations 42 CFR Part 66.

cell lines also exhibit limited in vitro proliferative capacity, as do fibroblast-like cells. Additional information regarding differentiated cells in culture may be obtained from the following references:

Jacoby, W. and I. Pastan (eds.). 1979. Methods in Enzymology. Cell Culture. L VIII, Section III, Academic Press.

Montagna, W., A.M. Kligman, K.W. Wuepper and J.P. Bentley (eds.). 1979. Proceedings of the 28th Symposium on the Biology of Skin. J. Invest. Dermatol. (special issue on aging):73.

Nichols, W.W. and D.G. Murphy (eds.). Differentiated Cells in Aging Research. Internat. Rev. Cytol. Supplement, 10.

Harris, C.C., B.S. Trump and G.D. Stoner (eds.). 1980. Cultured Human Tissues and Cells in Biomedical Reserch. Methods in Cell Biology, Volume 21, Parts A and B, Academic Press.

III. GOALS AND SCOPE

The goal of this announcement is to encourage research on the mechanisms of cellular aging. The use of differentiated cells in culture provides an excellent opportunity to study age-associated alterations in differentiated functions that are expressed by cells in vitro. Such studies could lead to an understanding of mechanisms of age-related functional decline in various tissues and organs.

IV. SPECIFIC OBJECTIVES

The NIA seeks research and research training grant applications in cellular aging, encompassing growth and nutrition, somatic cell genetics and various aspects of cellular, molecular and developmental biology pertaining to differentiated cells. Research is encouraged in, but not limited to, the following areas:

1. Age-related changes in structure and function of differentiated products (specific structural proteins and enzymes) and other biochemical properties of primary and secondary cultures.
2. Age-related changes in membrane structure and function affecting: inter- and intra-cellular communication; energy production; and antigenic, absorptive, receptor and other properties of the cell surface.
3. Age-related alterations in subcellular structures involved in motility, digestion, detoxification, secretion, and various synthetic functions of the cell.
4. Age-related changes in nuclear structure and function (e.g., chromatic structure; DNA replication and repair; regulation of gene expression; ribosome production; nuclear-cytoplasmic interactions; chromosomal aberrations and neoplastic transformation).

5. The relationship between in vitro and in vivo cellular aging as elucidated by cell and tissue transplantation and the use of chimeric and genetic mosaic animals.
6. The use of somatic cell genetics to understand the genetic basis of cellular aging and regulatory mechanisms of cellular growth relevant to the aging process.
7. The development of new strains of cells more differentiated than fibroblasts; this is especially important for human strains. Examples are human uterine smooth muscle cells and human aortic smooth muscle cells.
8. The requirements for establishment of normal differentiated cell strains capable of expressing differentiated traits (e.g., nutrition, growth factors, feeder layer, co-cultivation and other environmental conditions, such as oxygen tension, which affect culture growth) and perturbations or procedures that alter, inhibit or delay age-related changes in differentiated functions.

Although studies with cultured human cells (e.g., cells obtained from vascular and nervous tissues, gastrointestinal and urinary tracts, endocrine and exocrine organs, retina, lung, bone, muscle and skin) expressing tissue and organ specific functions are preferred, use of other vertebrate cell systems, including embryonic cells, may be desirable in some cases. The NIA maintains colonies of laboratory mice and rats of different ages. Applicants interested in using these animals must contact, prior to submitting applications:

Chief, Molecular and Cellular Biology Branch
Building 31 - Room 5C19
National Institute on Aging
Bethesda, Maryland 20205

Telephone: (301) 496-6402

To support research on cellular aging, the NIA has established, under contracts, an Aging Cell Repository. Additional information on these resources may be obtained from publications by N.K. Das and D.G. Murphy on the National Institute on Aging Cell Repository, (Exp. Aging Res. 4:321-331. 1978), available upon request from the Molecular and Cellular Biology Branch.

V. MECHANISMS OF RESEARCH AND RESEARCH TRAINING SUPPORT

The primary mechanisms for support of this program are:

1. Project Grant (the traditional NIH research support mechanism).
2. Postdoctoral Fellowship (the Individual National Research Service Award).

Additional mechanisms for support are:

3. Program Project Grant* (for multidisciplinary research involving several projects with a common focus).

4. New Investigator Research Award** (an optional, introductory grant mechanism; applicants may not have previously been supported as Principal Investigators by a U.S. Public Health Service research grant; ceiling \$30,000 per year for three years).
5. Clinical Investigator Award** (for clinically trained investigators; three years of support: salary up to \$30,000; supplies etc. up to \$10,000 annually).
6. Research Career Development Award
7. Institutional Training Grant* (Institutional National Research Service Award).

* Potential Applicants should contact NIA staff.

** Write NIA (see below) for information and instructions.

VI. REVIEW PROCEDURES AND FUNDING POLICY

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

VII. METHOD OF APPLYING

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

Office of Grant Inquiries
Division of Research Grants
National Institutes of Health
Bethesda, Maryland 20205

Telephone: (301) 496-7441

Please type the phrase NIA CELL BIOLOGY PROGRAM on the face page of the application. Enclose a cover letter indicating that the application is in response to this announcement.

Forward application to:

Division of Research Grants
National Institutes of Health
Westwood Building - Room 449
5333 Westbard Avenue
Bethesda, Maryland 20205

Application receipt dates for Research Project Grants and Special Research Awards are: July 1, November 1 and March 1.

Receipt dates for applications for individual or institutional National Research Service Awards, Program Project Grants, Clinical Investigator Awards, and Research Career Development Awards are: June 1, October 1 and February 1.

Prior to formal submission of an application, please send a letter of intent to the Cell Biology Program (see address below). Include name of principal investigator, institutional address, title of application, and abstract of proposed research.

VIII. INQUIRIES AND CORRESPONDENCE

Inquiries and correspondence should be directed to:

Dr. DeWitt G. Hazzard
Head, Cell Biology Program
Biomedical Research and Clinical Medicine
National Institute on Aging
National Institutes of Health
Building 31 - Room 5C15
Bethesda, Maryland 20205

Telephone: (301) 496-6402

or

Dr. Richard L. Sprott
Chief, Molecular and Cellular Biology Branch
Biomedical Research and Clinical Medicine
National Institute on Aging
National Institutes of Health
Building 31 - Room 5C19
Bethesda, Maryland 20205

Telephone: (301) 496-6402

NOTICE

AVAILABILITY OF UPDATED GUIDELINES FOR
COMPETING INSTITUTIONAL NRSA APPLICATIONS (T32)
TO BE SUBMITTED TO THE NATIONAL EYE INSTITUTE
NATIONAL EYE INSTITUTE

At its January 1983 meeting, the National Advisory Eye Council made a number of recommendations with respect to the consideration and funding of institutional T32 awards by the National Eye Institute (NEI). These recommendations have been incorporated in updated guidelines for NEI applicants, which have been distributed to NEI institutional T32 program directors. Other interested parties may receive copies of the revised guidelines or further information by writing to:

Ronald G. Geller, Ph.D.
Associate Director
Extramural and Collaborative Programs
National Eye Institute
National Institutes of Health
Building 31, Room 6A03A
Bethesda, Maryland 20205

NOTICE

AVAILABILITY OF PRIMARY REFERENCE MATERIALS

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

The National Heart, Lung, and Blood Institute (NHLBI) will provide Primary Reference Materials to qualified investigators studying blood material interactions. Polyethylene and polydimethylsiloxane are available without charge in limited amounts for use as calibration standards for physicochemical and biological characterization of biomaterials for cardiovascular applications. Investigators should designate a reproducible material to be used as a routine control (secondary reference material) in all studies; the Primary Reference Material is to be used to calibrate the secondary reference material and thereby assess stability of experimental procedures. The Primary Reference Materials are available as sheets (2.5 x 7.5 cm) or tubing (4 mm ID, 5 mm OD, 0.5 to 1.5 m length) and are individually packaged, sterilized, and characterized.

To receive Primary Reference Materials, investigators should submit the following information in a letter: a brief description of experimental design which discusses how primary and secondary Reference Materials will be employed; polymer requested, including configuration and size; identification of the laboratory's secondary reference material; and details of the methods to be used for physicochemical and/or biological characterization of both the NHLBI Primary Reference Material and the laboratory's secondary reference material. This letter should also indicate a willingness to return the data obtained with the primary and secondary reference materials. Preferred characterization methods are discussed in Guidelines for Blood-Material Interactions (NIH Publ. No. 80-2185) and Guidelines for Physicochemical Characterization of Biomaterials (NIH Publ. No. 80-2186); these guidelines and additional information regarding methods by which the materials are characterized before delivery are available upon request. Please submit requests and inquiries to:

Devices and Technology Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Federal Building - Room 312
7550 Wisconsin Avenue
Bethesda, Maryland 20205

Telephone: (301) 496-1586

NOTICE

AVAILABILITY OF PRIMARY REFERENCE MATERIALS

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

The National Heart, Lung, and Blood Institute (NHLBI) will provide Primary Reference Materials to qualified investigators studying blood material interactions. Polyethylene and polydimethylsiloxane are available without charge in limited amounts for use as calibration standards for physicochemical and biological characterization of biomaterials for cardiovascular applications. Investigators should designate a reproducible material to be used as a routine control (secondary reference material) in all studies; the Primary Reference Material is to be used to calibrate the secondary reference material and thereby assess stability of experimental procedures. The Primary Reference Materials are available as sheets (2.5 x 7.5 cm) or tubing (4 mm ID, 5 mm OD, 0.5 to 1.5 m length) and are individually packaged, sterilized, and characterized.

To receive Primary Reference Materials, investigators should submit the following information in a letter: a brief description of experimental design which discusses how primary and secondary Reference Materials will be employed; polymer requested, including configuration and size; identification of the laboratory's secondary reference material; and details of the methods to be used for physicochemical and/or biological characterization of both the NHLBI Primary Reference Material and the laboratory's secondary reference material. This letter should also indicate a willingness to return the data obtained with the primary and secondary reference materials. Preferred characterization methods are discussed in Guidelines for Blood-Material Interactions (NIH Publ. No. 80-2185) and Guidelines for Physicochemical Characterization of Biomaterials (NIH Publ. No. 80-2186); these guidelines and additional information regarding methods by which the materials are characterized before delivery are available upon request. Please submit requests and inquiries to:

Devices and Technology Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Federal Building - Room 312
7550 Wisconsin Avenue
Bethesda, Maryland 20205

Telephone: (301) 496-1586