Full Text DK-94-023

NUTRIENT MODULATION OF CELL INTEGRITY AND REPAIR MECHANISMS

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National Institute of Diabetes and Digestive and Kidney Diseases
National Cancer Institute
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National Institute of Allergy and Infectious Diseases
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Child Health and Human Development
National Institute on Deafness and Other Communication Disorders
National Institute of Dental Research
National Institute of Environmental Health Sciences
National Institute of Neurological Disorders and Stroke
Office of Research on Minority Health

Application Receipt Date: November 18, 1994

PURPOSE

This request for applications (RFA) is designed to encourage research grant applications focusing on mechanisms (primarily molecular and genetic mechanisms) that underlie nutrient modulation of cellular repair processes and maintenance of cellular integrity. Research should be aimed at

the normal processes involved in the effects of specific nutrients or their metabolites on cellular, genetic, and metabolic functions, as well as elucidation of defective mechanisms.
This initiative should offer unique opportunities afforded by the basic sciences and new technologies (e.g., molecular biology, NMR, ESR, PET) to enrich nutrition science. Nutrition science supported by the National Institutes of Health (NIH) includes studies designed to assess the consequences of food or nutrient intake, utilization in the intact organism, and the metabolic and behavioral mechanisms involved. Further support is needed for studies of nutrient variables at the cellular and subcellular levels; elucidation of the metabolic functions of nutrients in both animal models and humans; examination of genetic-nutrient-environmental interactions; and ultimately, studies of the role of diet in the maintenance of health, and the prevention and treatment of disease.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This RFA, Nutrient Modulation of Cell Integrity and Repair Mechanisms, is related to the priority areas of nutrition, physical activity and fitness, heart disease and stroke, cancer, and diabetes and chronic disabling conditions. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0) or "Healthy People 2000" (Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-783-3238).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign for-profit and non-profit organizations, public and private, such as universities, hospitals, laboratories, units of State and local government and eligible agencies of the Federal government. Foreign institutions are not eligible for the First Independent Research Support and Transition (FIRST) (R29) award. Applications from minority individuals and women are encouraged.

MECHANISM OF SUPPORT

The mechanisms available for support of applications in response to the RFA include research project grants (R01) and FIRST (R29) Awards. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. Awards will be administered under PHS grants policy as stated in the PHS Grants Policy Statement.

This RFA is a one-time solicitation. Generally, future unsolicited competing continuation applications will compete with all investigator-initiated applications and will be reviewed by a DRG study section. The total project period for an application submitted in response to the present RFA may not exceed five years. A maximum of three years may be requested for foreign awards. The maximum dollar request for R01s is limited to $160,000 in direct costs for the initial budget period. Applicants for R29s should refer to guidelines in the PHS 398 packet for preparation of budgets. The earliest possible award date will be July 1, 1995.

FUNDS AVAILABLE

The NIH will allocate approximately $4 million to support projects received in response to this RFA during FY 1995. It is anticipated that 20 to 25 awards will be made, provided that applications of sufficient scientific merit are received. Although this program is provided for in the financial plans of the NIH, the award of grants pursuant to this RFA is also contingent upon the availability of funds for this purpose. Subsequent support will be dependent upon submission of a renewal application through established NIH procedures for research grants related to nutrition.

RESEARCH OBJECTIVES

Background

The major objective of this initiative is to further encourage application of the basic sciences and new technologies (e.g., molecular biology, NMR, ESR, PET) to nutrition questions. Five of the ten leading causes of morbidity and mortality for Americans today are diet-related, including coronary heart disease, stroke, diabetes, and several forms of cancer. Among individuals with acquired immunodeficiency syndrome (AIDS), chronic diarrhea and wasting are important medical complications associated with impaired nutrient absorption. In addition, there is considerable diversity in response to nutrients in the human population, and special concerns exist for the groups that are most nutritionally vulnerable, that is, certain ethnic groups, premature infants, pregnant and lactating women, postmenopausal women, older persons, and immunocompromised individuals. Furthermore, there is strong evidence implicating nutritional factors in obesity, osteoporosis, malabsorption syndromes, immune function, and impaired muscular, sensory, and intellectual performance.

The genome is influenced by events occurring in utero during stages of development and throughout the life span of the maturing organism when molecular events can be altered by nutritional and other external factors. These events are a composite of interactions of

environmental, genetic, and metabolic processes. Mechanistic investigations are expected to lead to explanations of observations reported from clinical nutrition and epidemiological studies and to provide leads to effective interventions and rational therapies for individuals with chronic and acute diseases.

New methodologies based on molecular techniques have the potential to create new and more reliable indicators of nutrient requirements for optimal health and functional capacity. Newer technologies (NMR, ESR) have been developed that allow investigation of "in vivo" metabolism and interactions. Innovative utilization of technologies from other disciplines, but applied to nutritional investigations are encouraged. These methodologies should be used to increase understanding of nutrient-cell interactions that underlie the biological basis of the transition from healthy cells with normal biological functions to diseased cells with disturbed biological functions. The fundamental knowledge gained will ultimately be applied in clinical settings to treat or ameliorate disease and be translated to the general public.

Research Objective and Scope

Each of the Institutes and Centers at the NIH supports nutrition research related to its own mission and mandates. Nutrients have been shown to modulate or regulate the expression of genetic potential and to stimulate regulatory hormones, which in turn influences gene expression and the metabolic pathways. In bionutrition research, molecular biology and other newer technologies should be applied to the study of (a) intermediary metabolism; (b) the mechanisms of subcellular, cellular, and tissue responses to nutrient(s); and (c) the understanding of human genetic variation and the extent to which exposure to environmental factors modify normal physiological functions in an effort to ensure optimal outcomes in prevention and treatment of disease.

All applications should clearly identify the nature in which a dietary nutrient or functional component is a study parameter. Collaborative interactions between nutritional sciences investigators and those in other disciplines are encouraged to promote utilization of newer technologies, especially technologies not traditionally used for nutrition research. Furthermore, collaborative efforts that include interactions between the basic and clinical sciences are encouraged. Applications from new, independent investigators (at the FIRST (R29) award level) and applications that include newly established interactions and collaboration are also encouraged. The NIH expects to fund a range of nutrition research grants dealing with disease-related, age-related, and environment-related factors. Examples of relevant research topics are provided below. However, the list of examples is neither complete nor restrictive.

o The use of new technologies (e.g., electron spin resonance, NMR, PET) to investigate mechanisms of nutrient and nutrient metabolite interactions and functions in vivo, for example: antioxidant protection from lipoprotein oxidation and interactions of antioxidants and free radicals and other oxidative products

o Antioxidant or other nutrient-mediated protection against genetic damage

o Aging and disease-related alterations in antioxidant defense/prevention of oxidation and response to nutrient antioxidants

o Nutrient modulation of cell repair and regeneration, including cellular and/or tissue damage, which may be caused by environmental factors, and influence on mechanisms involved in cell death

o Nutritional interactions associated with molecular regulation/control of carcinogen activation, inhibition, or potentiation

o Nutritional control of cell differentiation, proliferation, and cellular/malignant transformation

o Nutrient influence on DNA repair and the role of nutrients in modulating gene expression

o Nutrient modulation of cell receptor expression and functions, including consequences from exposure to environmental agents

o Role of nutritional factors in the regulation of genes that control immune system structure and function

o Nutrient modulation/control of cell-cell signaling at the molecular level

o Influence of nutrients on the expression and action of regulators of cellular processes such as cytokines, lymphokines, and adhesion molecules

o Aging and disease-related changes in retinoid and vitamin D metabolism, cellular receptors, and expression of responsive genes

o Nutrient modulation of transport mechanisms at the molecular level, including consequences from exposure to environmental agents

o Nutritional approaches to ameliorate wasting in AIDS and other chronic disorders and to improve absorptive capabilities of damaged intestinal epithelium

o Studies on the potential alteration of nutrient requirements resulting from exposure to environmental agents

o Interactions between normal and abnormal neurological processes and nutrients

o Investigations that may identify genetic predisposition for differential nutrient needs or responsiveness among subpopulations based on gender or ethnic origin.

STUDY POPULATIONS

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This new policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43) supersedes and strengthens the previous policies (Concerning the Inclusion of Women in Study Populations, and Concerning the Inclusion of Minority in Study Populations) which have been in effect since 1990. The new policy contains some new provisions that are substantially different from the 1990 policies.

All investigators proposing research involving human subjects should read the "NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research," which was reprinted in the Federal Register of March 28, 1994 (59 FR 14508-14513) to correct typesetting errors in the earlier publication, and reprinted in the NIH GUIDE FOR GRANTS AND CONTRACTS of March 18, 1994, Volume 23, Number 11.

Investigators may obtain copies from these sources or from the program staff or contact person listed below. Program staff may also provide additional relevant information concerning the policy.

APPLICATION PROCEDURES

The research grant application form PHS-398 (rev. 9/91) is to be used in applying for these grants. The form is available from most institutional offices of sponsored research and from the Office of Grants Information, Division of Research Grants, National Institutes of Health, 5333 Westbard Avenue, Room 449, Bethesda, MD 20892, telephone 301/435-0714.

The RFA label available in the PHS 398 application form must be affixed to the bottom of the face page. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2a of the face page of the application form and check the YES box.

Submit a signed, typewritten original of the application, including the Checklist, plus five signed, exact photocopies, in one package to:

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

Applications must be received by November 18, 1994. If an application is received after that date, it will be returned to the applicant. The Division of Research Grants (DRG) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, it is allowable to submit the same project as both an R01 or R29 and as a component project of a program project. The DRG will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications previously reviewed. Such applications must not only include an introduction addressing the previous critique but also be responsive to this RFA.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. If so, a letter of agreement from either the GCRC program director or principal investigator could be included with the application.

FIRST (R29) award applications must include at least three sealed letters of reference attached to the face page of the original application. FIRST (R29) award applications submitted without the required number of reference letters will be considered incomplete and will be returned without review.

REVIEW CONSIDERATIONS

Upon receipt, applications will be initially reviewed by the DRG for completeness. Incomplete applications will be returned to the applicant without further consideration. Evaluation for responsiveness to the program requirements and criteria stated in the RFA is an NIH staff function. If the application is not responsive to the RFA, NIH staff will contact the applicant to determine whether it should be returned to the applicant, or whether it should be held until the next regular receipt date and reviewed in competition with all other applications.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the ICDs in accordance with the review criteria stated below. As part of the initial merit review, a process (triage) may be used by the initial review group in which applications will be determined to be competitive or non-competitive based on their scientific merit relative to other applications received in response to the RFA. Applications judged to be competitive will be discussed and be assigned a priority score. Applications determined to be non-competitive will be withdrawn from further consideration and the Principal Investigator and the official signing for the applicant organization will be notified.

Those applications judged to be competitive will be reviewed for scientific and technical merit in accordance with the usual NIH peer review procedures by an initial review group specifically convened for this RFA. Following this review, the applications will be given a secondary review by an Institute Advisory Council/Board unless not recommended for further consideration by the initial review group.

Review criteria for this RFA are generally the same as those for unsolicited research grant applications.

o scientific/technical merit criteria specific to the objectives of the RFA;

o scientific, technical, or medical significance and originality of proposed research;

o appropriateness and adequacy of the experimental approach and methodology proposed to carry out the research;

o qualifications and research experience of the Principal Investigator and staff, particularly, but not exclusively in the area of the proposed research;

o availability of resources necessary to perform the research;

o appropriateness of the proposed budget and duration in relation to the proposed research; and

o if an application involves activities that could have an adverse effect upon humans, animals, or the environment, the adequacy of the proposed-means for protecting against or minimizing such effects.

AWARD CRITERIA

The anticipated date of award is July 1, 1995. The following will be considered in making funding decisions.

o Quality of the proposed project as determined by peer review
o Availability of funds
o programmatic balance among the studies recommended for funding.

INQUIRIES

Written and telephone inquiries concerning this RFA are encouraged.
Inquiries regarding programmatic issues may be directed to:

Michael K. May, Ph.D.
Division of Digestive Diseases and Nutrition
National Institute of Diabetes and Digestive and Kidney Diseases
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Jerry Robinson, Ph.D.
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Bethesda, MD 20892-9165
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Inquiries regarding fiscal matters may be directed to:

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Division of Extramural Activities
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Schedule

Application Receipt Date: November 18, 1994
Initial Review: February/March 1995
Second Level Review: May/June 1995
Anticipated Date of Award: July 1, 1995

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.848. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 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 Public Health Service strongly encourages all grant recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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