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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.

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NOTICES

EXPEDITED REVIEW OF FELLOWSHIP APPLICATIONS

P.T. 22; K.W. 0720005, 1014002

Division of Research Grants

Currently, the review and award cycle for the National Research Service Award Individual fellowship (F32) takes approximately 8 months. Reducing this time would be beneficial for applicants, because in the early stages of their careers, they often need the assurance of future fellowship support before moving to new positions or planning for the future. Similarly, sponsors of fellows need to know whether support would be available to continue their research training efforts.

Based on the recommendations of several Division of Research Grant (DRG) committees, changes are being made to expedite the review of individual fellowship applications. These changes include streamlining of the receipt and referral of applications, and abbreviation of the summary statement. The changes should decrease the time required for review by approximately 2 months.

With the changes in the receipt and referral procedures that have been initiated, the work of the study section (administrative review of the applications, assignment to reviewers, formation of committees, and mailing of applications) can be initiated at an earlier time. In addition, a simplified evaluation format will be introduced, which will include only evaluative statements regarding the candidate, the scientific merit and training potential of the research proposal, the training resources and environment, and a resume. This simplified review or assessment form will not only ease the burden for reviewers, but also permit more rapid preparation of summary statements.

Letters of reference should accompany the application at the time of submission to facilitate the process. DRG has notified potential applicants through the NIH Guide for Grants and Contracts (Vol. 17, No. 10, March 18, 1988), that at least three completed, sealed letters of reference must be submitted with each individual fellowship application, beginning with the May 10, 1988 receipt date. These procedures will save time in processing applications and ensure that the required information is included with the application.

The accelerated review of fellowship applications also will require a new schedule of study section meeting dates. Under the proposed changes, study section meetings for the January 10, May 10, and September 10 receipt dates (which will remain unchanged) will take place in late March/April, mid July, and mid November, respectively. Summary statements will be completed by May, August, and December, respectively, and the entire initial review cycle will be reduced approximately 2 months.

CLINICAL CENTERS FOR A REGISTRY OF PATIENTS WITH SEVERE CONGENITAL DEFICIENCY OF ALPHA1-ANTITRYPSIN

P.T. 04; K.W. 0715165, 0785035, 0780000

National Heart, Lung, and Blood Institute

The Division of Lung Diseases, National Heart, Lung, and Blood Institute is establishing a registry of patients with severe congenital deficiency of alpha1-antitrypsin (plasma levels <50 mg/dl) including those receiving replacement therapy with intravenous preparation of alpha1-proteinase inhibitor. The purpose of this announcement is to provide information to clinical centers interested in participating in the registry.

The Food and Drug Administration recently approved an intravenous preparation of human plasma derived alpha1-proteinase inhibitor concentrate for replacement therapy in individuals with the genetic deficiency. This approval was based on laboratory evidence of biochemical efficacy of the treatment, i.e., achievement of theoretically protective levels of the proteinase inhibitor in the lung following intravenous administration. A variety of clinical, logistical and other factors stand in the way of a controlled clinical trial. However, the Division of Lung Diseases, NHLBI, has decided to sponsor a patient registry to characterize the clinical and laboratory course of severe congenital deficiency of alpha1-antitrypsin whether or not the patient is undergoing long-term replacement therapy.

An important organizational component of this registry will be the group of voluntarily participating clinical centers which will provide patient data to be entered into the registry. NHLBI will identify a number of such centers around the country based on availability of potential patients who meet the registry criteria and demonstrated ability to perform high quality pulmonary function tests.

NHLBI is separately issuing a request for proposals for a clinical coordinating center to manage the registry and to collect data from the participating centers. The registry will be conducted according to a protocol developed by the NHLBI in consultation with a committee of experts. A copy of the draft summary protocol is available upon request. The data to be submitted to the registry will be information often gathered as part of the routine monitoring of the patients. Confirmation of the Pi-phenotype of the patient (through a central laboratory which will be established for the registry) will be required for entry. NHLBI will not provide funds for patient care or research in this registry, but it will pay for the submission of completed data forms and the specified spirometric records (\$100 on entry and \$50 at annual follow-up for each subject). The patient recruitment phase is expected to last for 2 years and each subject enrolled will be followed for 3-5 years.

Pulmonary centers interested in being considered as one of the clinical centers should contact the NHLBI program office mentioned below. The commitment of the centers would be to enter at least 10 homozygous alpha₁-antitrypsin deficient patients, whether on replacement therapy or not, into the registry over a 2 year period and to follow these individuals for 3 to 5 years. The patients entered through a center could be those followed at the center or those followed by other physicians in the area provided that the pulmonary function tests required by the protocol are done at the center. The participating centers would be undertaking the responsibility of ensuring that all of the tests required are performed and necessary clinical data are collected in accordance with the manual of procedures that we provide.

The participating centers will be provided semiannual summaries of the progress of the registry. A meeting of investigators from the participating clinical centers and the clinical coordinating center will be held annually (in conjunction with the ALA/ATS meeting) to assess progress of the registry and to exchange pertinent scientific information.

For further information please contact the NHLBI program office at the following address:

Zakir H. Bengali, Ph.D.
Airways Diseases Branch
Division of Lung Diseases
National Heart, Lung, and Blood Institute
Westwood Building, Room 6A16
5333 Westbard Avenue
Bethesda, Maryland 20892
Telephone: (301) 496-7332

PHS GRANT APPLICATION FORM 398--REMINDERS

P.T. 34; K.W. 0710030, 1014002

National Institutes of Health

The newly revised form PHS 398 (dated 9/86) must be used by all NRSA Institutional Training Grant applicants. This requirement started with the January 10, 1988 receipt date. The revised form must also be used by all research grant applicants. This requirement starts with the February 1, 1988 receipt date. THE PAGE LIMITATIONS INDICATED IN THE INSTRUCTIONS FOR THE 9/86 REVISION MUST BE OBSERVED. ANY APPLICATION SUBMITTED ON ANY VERSION OF THE PHS 398 OTHER THAN THE 9/86 REVISION WILL BE RETURNED WITHOUT REVIEW, AS WILL APPLICATIONS THAT EXCEED THE PAGE LIMITS SPECIFIED IN THE PHS 398 INSTRUCTIONS OR SUPPLEMENTAL INSTRUCTIONS PERTAINING TO A PARTICULAR PROGRAM.

It is important to submit legible copies of the application. The original pages of the PHS 398 form, printed in orange ink, should be used. However, if these pages are not reproducible by any copying machine available to your institution, you may substitute the draft pages of the form (which are in black ink) after deleting the words "Remove and Use for Draft Copy" in the margin. DO NOT SUBSTITUTE THE 5/82 VERSION OF THE PHS 398 form. An application will be considered incomplete and returned if the original and all copies are not legible.

HUMAN LIVER FOR SCIENTIFIC INVESTIGATION

P.T. 34; K.W. 0745065, 0765035, 0780000

National Institute of Diabetes and Digestive and Kidney Diseases

The Liver Tissue Procurement and Distribution System (LTPADS) is an NIH service contract to obtain human liver from 5 regional centers for distribution to scientific investigators throughout the United States. These 5 regional centers have active liver transplant programs which have human subjects approval to provide portions of the resected pathologic liver for which the transplant is performed. Human pathologic liver prepared according to the investigator's specifications provides the opportunity to verify if animal liver investigations are relevant to human liver pathophysiology. The preparation of these livers has been excellent for the usual molecular biologic techniques. Therefore, we are primarily interested in soliciting proposals from investigators interested in studying pathologic liver specimens. Examples would include a particular metabolic disorder or disease process or the general process of cirrhosis. At present time, we are predominantly supplying "normal" human liver specimens to a significant number of investigators. However, for obvious reasons, this supply is extremely limited in contrast to the pathologic livers readily available at the time of liver transplant. Further information and proposal forms for interested investigators can be obtained from:

Harvey L. Sharp, M.D.
Principal Investigator, LTPADS
c/o Elizabeth Webster
Box 279 Mayo Bldg.
University of Minnesota Hospitals
Minneapolis, Minnesota 55455
Telephone: (612) 624-1133

DATED ANNOUNCEMENTS (RFPs AND RFAs)

THE PRETHROMBOTIC STATE IN MALIGNANCY

RFA AVAILABLE: 88-HL-6-B

P.T. 34; K.W. 0715040, 0715035, 0765035, 1003002

National Heart, Lung, and Blood Institute

Application Receipt Date: September 19, 1988

The Blood Diseases Branch of the Division of Blood Diseases and Resources, National Heart, Lung and Blood Institute (NHLBI), announces the availability of a Request for Applications (RFA) on the above subject. Copies of the RFA are currently available from staff of the NHLBI.

The program will support research designed to reveal the mechanisms underlying the prethrombotic state in malignancy, a state which precedes the development of a frank thrombotic episode and which is now possible to quantitate. Abnormalities of the hemostatic system that might be expected to increase the likelihood of thrombosis, either by virtue of increasing fibrin formation or by decreasing the potential for fibrinolysis is herein referred to as the prethrombotic state. It is expected that applications in response to this RFA will propose research that delineates in precise physiologic and biochemical terms, alterations of the hemostatic system that occur upon exposure to specific tumor cell components and relates these alterations to clinically observable thrombotic events. It is anticipated that up to six grants will be awarded under this program.

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.

Requests for copies of the RFA should be addressed to:

Diane L. Lucas, Ph.D.
Blood Diseases Branch
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute
Federal Building, Room 5A12
National Institutes of Health
Bethesda, Maryland 20892
Telephone: (301) 496-5911

IDENTIFICATION OF GENETIC ALTERATIONS INVOLVED IN BLADDER CARCINOGENESIS

RFA AVAILABLE: 88-CA-05

P.T. 34; K.W. 0705075, 0715035, 1002058, 1002008, 1003012, 0710030

National Cancer Institute

Application Receipt Date: July 7, 1988

The Organ Systems Program, through the National Cancer Institute (NCI), Division of Cancer Prevention and Control, invites grant applications from organizations which are capable of developing multi-disciplinary research programs involving specialists in molecular biology, chemical carcinogenesis and organic chemistry. The major goal of this initiative is to increase understanding of the genetic alterations underlying multistage chemical carcinogenesis in the urinary bladder. A renewed experimental approach to this goal is made possible by recent successes in developing molecular, cellular, and in vivo systems for the exploration of urinary bladder carcinogenesis. There is a unique opportunity to integrate these areas of research in efforts to achieve the following specific objectives: (1) determine which alterations (mutations, translocations, amplifications) in known cellular proto-oncogenes are important in multi-stage bladder carcinogenesis in experimental systems; (2) identify genes which might be involved in the pathogenesis of bladder cancers; (3) use cytogenetic studies to provide clues to the molecular alterations in bladder cancer cells; (4) determine the mechanisms by which carcinogens activate proto-oncogenes in bladder tumorigenesis; and (5) determine the roles and timing of genetic changes during the multi-stage development of bladder neoplasia.

OBJECTIVE AND SCOPE

This RFA is intended to initiate studies of the bladder in organizations which are already contributing significantly to research in molecular biology. An organization with a molecular biology laboratory, which can establish associations with research efforts in chemical carcinogenesis and bladder cancer, is encouraged to respond to this RFA. At the time of submission, core support for molecular biology, qualified investigators, technical expertise and facilities should exist in the organizations which respond to this RFA.

The purpose of this initiative is to stimulate research on molecular genetic and cytogenetic mechanisms of bladder carcinogenesis. Several model systems already exist for studying chemical carcinogenesis in the mammalian urinary bladder. Responses to this RFA might incorporate such systems, e.g., make use of models for multi-stage transformation. Other systems might be developed which could facilitate experimental approaches to understanding how genetic alterations are involved in the genesis and development of bladder tumors. Either animal or cell culture models (human or rodent) could be used, as long as the system studied has well defined biologic endpoints.

Highest priority should be placed on approaches which are likely to provide detailed molecular information pertinent to bladder tumor induction. Attempts might be made to elicit biologic responses with metabolites of carcinogens which are subject to metabolic activation in urinary bladder cells, as for example N-hydroxyarylamine derivatives. This would avoid the possibility that the target bladder cells could respond because of inadequate levels of N-oxidation potential. It is envisioned that it should be possible to employ DNA vectors which carry the potential for eliciting cellular transformation, e.g., proto-oncogenes, when modified by carcinogens. This approach should permit the direct exploration of biologic responses to carcinogens introduced into the DNA at single, specific sites, following transfection into mammalian cells.

Transformed cells should be analyzed for alterations in cellular genes thought to be important in the neoplastic process. This would involve analysis of isolated DNA and the use of in situ hybridization techniques. The technology employed should be able to detect base substitutions, frameshifts, translocations, amplifications and loss of genes (or their reduction to

homozygosity). The altered expression of specific genes, in the apparent absence of direct genetic alteration of the genes, might provide avenues of investigation into alternative control sequences.

The proposed studies should represent a multi-disciplinary effort, possibly involving collaboration among pathologists, molecular biologists, tumor biologists, cytogeneticists, organic chemists and experts in chemical carcinogenesis.

BACKGROUND

A search for activated cellular oncogenes in human bladder cancers has been somewhat successful. The first activated ras gene was discovered in a human bladder cancer cell line, and a subsequent search for such genes in fresh clinical biopsies of human bladder cancers showed activated ras genes present in about 10% of cases. Thus, the examination of bladder cancers with a view to identifying additional activated genes is relevant and important. Furthermore, the current association of ras with a small but significant percentage of human bladder cancers deserves further investigation. Ras activation has not been rigorously demonstrated to be causally associated with the development of bladder cancer. Also, the stage in development of bladder cancer at which ras might be activated has not been identified. Since bladder cancers are typically multi-stage, this information has possible relevance to understanding the etiology of the disease, and to developing molecular markers for diagnosis and prognosis.

Bladder urothelium is a useful tissue system for studies of multi-step chemical carcinogenesis because development of bladder cancer is characteristically multistage in nature. Epidemiologic evidence associates an increased risk for bladder cancer with exposure to environmental chemicals, particularly exposure to compounds which are classified as aromatic amines. Tumors have been induced using several important classes of chemical carcinogens including nitrosoureas, nitrofurans, polycyclic hydrocarbons and arylamines. Excellent rodent model systems have been developed to study the pathogenesis of bladder cancers induced by such carcinogens. These models have special advantages for study of the activation of cellular proto-oncogenes. For example, tumors of different grades and stages and of different histopathologies are obtained with these systems, and an analysis of such tumors could be useful for correlating molecular change with tumor pathology.

ELIGIBILITY

Applications must be responsive to the program goals of this RFA. Applicant organizations are required to have an active program in research in molecular genetics and to have the capacity for establishing liaison with investigators involved in research in chemical carcinogenesis, organic chemistry and bladder cancer. The applicant organization should be involved in treating bladder cancer patients or have the capacity to establish liaison with such an organization.

APPLICATION SUBMISSION AND REVIEW

This RFA solicitation is a single competition and has one specific deadline for receipt of applications. All applications responsive to this RFA will be reviewed according to the stated RFA review criteria by an appropriate peer review group composed primarily of non-Federal experts and set up by the Division of Extramural Activities, National Cancer Institute. Applications will be reviewed in competition with each other on a nationwide basis. A second review will be provided by the National Cancer Advisory Board.

A potential applicant organization is encouraged, but is not required, to submit a letter of intent and is encouraged to consult with NCI staff by telephone before submitting. The letter of intent is requested by May 6, 1988. It will not enter into the review of an application submitted in response to this RFA.

MECHANISM OF SUPPORT

The mechanism of support for this program is the NIH investigator-initiated research grant (R01). This type of solicitation is used when the NCI, with concurrence of a Board of Scientific Counselors, wishes to stimulate investigator interest in an important and opportune area of research. Awards can be made to non-profit and profit organizations. An applicant organization may apply for a period of support of up to three years under this RFA.

Contingent upon the continued availability of funds and dependent upon the receipt of a sufficient number of applications of high scientific merit, it is

anticipated that five awards will be made at an overall annual total cost of approximately \$650,000.

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.

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

William E. Straile, Ph.D.
Cancer Centers Branch
Division of Cancer Prevention and Control
National Cancer Institute
Blair Building, Room 727
8300 Colesville Road
Bethesda, Maryland 20892-4200
Telephone (301) 427-8818

ONGOING PROGRAM ANNOUNCEMENTS

OPPORTUNITIES FOR U.S. SCIENTISTS TO STUDY IN JAPANESE INSTITUTIONS

P.T. 22, 48; K.W. 0720005, 0404000, 0710030

Fogarty International Center

The Japan Society for the Promotion of Science (JSPS) recently established a postdoctoral research fellowship program in the biomedical sciences for U.S. scientists. The purpose of these fellowships is to provide a research experience in the biomedical and behavioral sciences in Japanese laboratories. The types of activity supported by this program include collaboration in basic or clinical research, and familiarization with or utilization of special techniques and equipment not otherwise available to the applicant. The program does not provide support for activities that have as their principal purpose brief observational visits, attendance at scientific meetings, or independent study.

The Fogarty International Center, National Institutes of Health, selects candidates for the program which is administered by the JSPS.

ELIGIBILITY

Applicants for the program must meet the following requirements:

- o be a U.S. citizen or permanent U.S. resident,
- o hold a doctorate in one of the clinical, behavioral or biomedical sciences,
- o be 35 years or younger at the start of the fellowship tenure.
- o make prior arrangements with the Japanese host researcher as to research plan.

SUPPORT

The JSPS will provide the following support:

- o monthly subsistence allowance of 270,000 yen;
- o monthly family allowance of 50,000 yen;
- o monthly housing allowance not to exceed 100,000 yen;
- o relocation allowance of 200,000 yen;
- o roundtrip economy class air fare expenses
- o in-transit travel allowance (transportation from Tokyo to destination, it other than Tokyo);
- o medical and accident insurance coverage for the fellow only;
- o language training allowance not to exceed 500,000 yen.

The Japanese Ministry of Education, Science and Culture will provide a research grant of up to 1.2 million yen to the fellow and sponsor to support the research effort.

APPLICATION AND SELECTION

The Japan Society for the Promotion of Science has two mechanisms by which U.S. scientists may apply for fellowships--through application to the Fogarty International Center or through an application submitted to JSPS on behalf of a U.S. scientist by a senior Japanese colleague.

A. Application Through the Fogarty International Center

Information and application kits are provided by the Fogarty International Center and are available between December 1 and April 30. The deadline for receipt of applications is May 10. Applications will be reviewed in the usual manner for scientific merit by a study section of the Division of Research Grants. The Fogarty International Center will transmit the applications of recommended candidates to JSPS in October. The JSPS will notify candidates of the results within two months of receiving recommendations from the Fogarty International Center. Those applicants who were not recommended for fellowships will be notified by the Fogarty International Center.

B. Nomination by Japanese Colleagues

The JSPS will accept nominations from senior Japanese scientists who wish to invite U.S. scientists to their laboratories. U.S. scientists interested in applying for a fellowship through this mechanism must contact their Japanese colleagues for additional information.

DURATION OF FELLOWSHIP

Fellowships are awarded for a one-year period, but extensions may be considered if recommended by the host institution and approved by the JSPS. The starting date of the fellowship is set by mutual agreement between the fellow and the host and must be within the twelve month period following the date of the award.

INQUIRIES AND APPLICATION KITS

Additional information or application kits should be requested from:

Lynn M. Amende, Ph.D.
Program Officer
International Research and Awards Branch
Fogarty International Center
National Institutes of Health
Bethesda, Maryland 20892
Telephone: (301) 496-1653

Note: A similar JSPS postdoctoral research fellowship program for engineers and scientists in disciplines other than biomedical, behavioral, and clinical sciences is available through by the National Science Foundation. Information and application kits may be obtained from:

Dr. Charles Wallace
or
Dr. Larry Weber
National Science Foundation
Washington, D.C. 20550
Telephone: (202) 357-9558

RESEARCH ON OSTEOARTHRITIS

P.T. 34; K.W. 0715010, 0755030, 0785055, 0745055, 0710030

National Institute of Arthritis and Musculoskeletal and Skin Diseases

PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute on Aging (NIA) invite grant applications to study a broad range of basic and clinical topics related to osteoarthritis. Support will be through individual research, fellowship training and career development grants.

BACKGROUND

Osteoarthritis is a disease of unknown etiology characterized by slowly developing local joint pain, stiffness, limitation of motion and deformity. These symptoms may represent a common final pathway for many pathophysiological conditions. Alteration and deterioration may occur in many of the component tissues and structures within the affected joint. Osteoarthritis is one of the most common of all chronic diseases and the most frequent rheumatic disease. It may affect one joint, a few or many. Approximately 16 million Americans have osteoarthritis as identified through a medical examination and history. Approximately 37 percent of the adult U.S. population have radiologic evidence of osteoarthritis in their hands and/or feet. About 23 percent of these radiologically-identified changes are classified as being moderate or severe.

To help stimulate and focus the desired goal of enhanced research efforts, the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institute on Aging (in conjunction with support from several private organizations) sponsored a Workshop on Osteoarthritis on July 21-25, 1985. A primary objective of the workshop was to develop suggestions for future research directions and approaches for achieving this new knowledge. Proceedings of the Workshop on Osteoarthritis were published in the Journal of Rheumatology (Volume 13, No. 6, pp 1127-1160 1986). This article documented over 130 recommendations for research by the workshop participants. A synopsis of the research suggestions is presented by the editors of the article in a concise list of 18 research areas to be pursued. Multidisciplinary approaches for research on osteoarthritis were emphasized. Investigators interested in responding to this announcement are invited to write or call the NIH program staff (listed in this announcement) to receive a copy of the journal article.

OBJECTIVES

This solicitation is intended to stimulate research that provides an improved understanding of general and age-specific epidemiology, etiology (including any age-related changes in function or metabolism) and prevention and treatment of osteoarthritis. Both basic and clinical research are encouraged. In many instances, collaborative and multidisciplinary research efforts may be required to achieve significant scientific advances. Research training and career development opportunities would be valuable for young investigators seeking to enter this field or to enhance their skills to conduct research related to osteoarthritis.

SCOPE

There is great need for increased research efforts in a broad range of scientific topics related to the pathogenesis, prevention and treatment of osteoarthritis. The scope of areas requiring further research was clearly described at the Workshop on Osteoarthritis. No priority has been established among the research suggestions presented in the article. Applications are encouraged in any scientifically meritorious research areas related to osteoarthritis.

The NIH urges applicants for grants to give added attention (where feasible and appropriate) to the inclusion of minority groups and/or women in the study populations for research.

APPLICATION AND REVIEW PROCEDURES

Applications in response to this announcement will be reviewed in accordance with the usual Public Health Service peer review procedures for research grant applications. Review criteria include the significance and originality of the research goals and approaches; feasibility of the research and adequacy of the experimental design; training research competence, and dedication of the investigator(s); adequacy of available facilities; provision for the humane care of animals; and appropriateness of the requested budget relative to the work proposed. Funding decisions will be based on the evaluations by the Initial Review Groups and the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council and the National Advisory Council on Aging recommendations. Applications should be submitted using form PHS-398, Rev. 9/86, available in the business or grants office at most academic or research institutions, or from the Division of Research Grants, National Institutes of Health.

Applications will be accepted in accordance with the dates for receipt of new applications on a continuing basis:

February 1, June 1, October 1

The phrase "RESPONSE TO NIAMS/NIA PROGRAM ANNOUNCEMENT: RESEARCH ON OSTEOARTHRITIS" should be typed on line 2 of the face page of the application. The original and six copies of the application should be sent or delivered to:

Grant Application Receipt
Office Division of Research Grants
Westwood Building, Room 240
National Institutes of Health
Bethesda, Maryland 20892-4500**

For further information, investigators are encouraged to contact the following individuals:

Stephen L. Gordon, Ph.D.
Musculoskeletal Diseases Program Director
National Institute of Arthritis and
Musculoskeletal and Skin Diseases
Westwood Building, Room 407
Bethesda, Maryland 20892-4500
Telephone: (301) 496-7326

Lawrence Petrucelli, Ph.D.
Arthritis Program Director
National Institute of Arthritis and
Musculoskeletal and Skin Diseases
Westwood Building, Room 405
Bethesda, Maryland 20892-4500
Telephone: (301) 496-7326

Ann Sorenson, Ph.D.
Osteoporosis and Rheumatology
Program Director
National Institute on Aging
Building 31, Room 5C-25
Bethesda, Maryland 20892-4500
Telephone: (301) 496-1033

This program is described in the Catalog of Federal Domestic Assistance No. 13.846, Arthritis, Musculoskeletal and Skin Disease Research and 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. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

ASSOCIATION OF ARTHRITIS AND MUSCULOSKELETAL DISEASES WITH HIV POSITIVITY AND AIDS

P.T. 34; K.W. 0705050, 0715010, 0715120, 0785055

National Institute of Arthritis and Musculoskeletal and Skin Diseases

The Arthritis and Musculoskeletal Programs of the National Institute of Arthritis and Musculoskeletal and Skin Diseases invite grant applications to carry out studies of arthritis and musculoskeletal conditions and their association with HIV infection and/or frank AIDS. This Program Announcement is to encourage research grant applications for basic, clinical and epidemiologic research. Research mechanisms to support these investigations include regular research grants (R01), Clinical Investigator Awards (K08), First Independent Research Support and Transition (FIRST) Awards (R29), and Postdoctoral Individual National Research Service Awards (F32).

Investigators from several laboratories have recently reported the co-occurrence of HIV antibody positivity or frank AIDS with Reiter's syndrome and other arthritides. It is unknown whether a biological connection exists between certain arthritides and HIV infection or whether some of these co-occurrences are merely coincidental.

Certain arthritides and musculoskeletal conditions may be found more frequently in HIV-positive individuals and AIDS patients than in the general population according to reported observations. The frequency, spectrum and natural history of these conditions in HIV-positive individuals, including AIDS cases are unknown. It has also been noted that a spectrum of disease encompassing Reiter's syndrome and psoriasis in particular, appears to be more severe and increasingly difficult to control as signs of immunodeficiency develop.

Safety and efficacy of drugs used in the management of arthritis and musculoskeletal conditions have not been formally assessed in HIV-positive individuals. Recent case reports have suggested that immunosuppressive drugs, particularly methotrexate, used widely at present in the management of rheumatoid arthritis and psoriatic arthritis may accelerate AIDS in HIV-infected individuals.

This solicitation is intended to stimulate basic, clinical and epidemiologic research related to arthritis and musculoskeletal diseases in HIV-positive individuals, including those who have AIDS. In addition, it is hoped that the increased frequency of these diseases in HIV-positive individuals will provide unusual opportunities for research on the pathogenesis and accelerating factors in Reiter's syndrome and other rheumatic diseases of uncertain etiology.

Among the broad spectrum of basic research projects encouraged are studies of disease pathophysiology and genetics. Clinical studies may include prevention of morbidity and mortality or amelioration of arthritis and musculoskeletal complications. Epidemiologic studies may focus on etiology, risk factors for disease development and severity, natural history of disease, prognosis for developing disease. This includes both AIDS and arthritis and musculoskeletal diseases, as well as descriptive studies of incidence, prevalence, morbidity and mortality.

The NIH encourages applicants to consider the inclusion of women and minorities in the study populations for all clinical research efforts, excepting studies involving pregnant women which may expose the fetus to undue risks. Gender and racial differences should be noted and evaluated. If women or minorities are to be excluded, a clear rationale should be provided for their exclusion.

Investigators are encouraged to work with existing, or proposed, longitudinal data collection resources and cohorts of patients. Populations which may be included are those at increased risk for HIV infection, as well as HIV-positive cohorts who are clearly defined by their source of exposure. Investigators are encouraged to use existing cohorts, such as the Multicenter AIDS Cohort Study (MACS), the HIV Pulmonary Complications Study and the AIDS Clinical Trials Group patients.

ELIGIBILITY

Non-profit organizations and institutions, governments and their agencies, for-profit organizations, and individuals are eligible to apply.

DEADLINE

Applications will be accepted in accordance with the announced receipt dates for new applications, listed in application kits numbered PHS-398, Rev. 9/86. Also, applicants have the option of submitting AIDS investigator-initiated R01 and R29 applications to the Division of Research Grants on May 1, September 1, or January 2 of each year for expedited review.

REVIEW PROCEDURES AND CRITERIA

Applications should be submitted on Form PHS-398, Rev. 9/86, or form 416-1 Rev. 6/85 (for F32), which are available in the institution's collaborative research or business office. Additional application kits may be obtained from the office of Grants Inquiries, Division of Research Grants (DRG), NIH. The phrase "Prepared in Response to Research Grants Announcement on Association of Arthritis and Musculoskeletal Diseases with HIV Positivity and AIDS" should be typed on line 2 of the first page of the application or item 3 of the 416-1. The original and six copies of the form 398 application or the original plus two copies of the form 416-1 should be sent to:

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

If expedited review is requested, the original plus 32 copies of R01 or R29 applications should be submitted.

Applications in response to this solicitation will be reviewed on a nationwide basis in competition with other research grant applications, and in accord with the expedited NIH peer review procedures for AIDS-related research. In order to expedite the review, PHS human subject certifications and animal verifications should be submitted with the applications. Applications will

first be reviewed for technical merit by initial review groups and then by the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council. The review criteria customarily employed by the NIH for regular research grant applications will prevail.

Applications from institutions which have a General Clinical Research Center (GCRC) funded by the NIH Division of Research Resources may wish to identify the Center as a resource for conducting the proposed research. In such a case, a letter of agreement from the Program Director of the GCRC should be included with the application material.

All PHS and NIH grant policies governing regular research project grants apply to applications received in response to this Program Announcement. Applications will be referred in accordance with normal of the NIH Division of Research Grants.

For further information contact:

Lawrence M. Petrucelli, Ph.D.
Arthritis Program Director
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 405
Bethesda, Maryland 20892
Telephone: (301) 496-7326

Reva C. Lawrence, M.P.H.
Epidemiology/Data Systems Program Officer
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Building 31, Room 4C07
Bethesda, Maryland 20892
Telephone: (301) 496-0434

MOLECULAR GENETICS OF THE MAMMALIAN SEX CHROMOSOMES AND AGING

P.T. 34; K.W. 1002058, 0710010

National Institute on Aging and
National Institute of Child Health and Human Development

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, the Genetics and Molecular Biology Programs of the Molecular and Cell Biology Branch of the NIA support research on the genetic and molecular mechanisms of aging.

The National Institute of Child Health and Human Development (NICHD) was established in 1962, to conduct and support research and training on biological and behavioral aspects of human development and reproduction. In keeping with this mandate, the Reproductive Genetics and Immunology Program of the Reproductive Sciences Branch (RSB) supports research and training on the genetic aspects of sex determination, sex differentiation, gonadal development, function and disorders.

The purpose of this Announcement is to encourage further research and training activities, using modern methods of genetics and molecular biology, to understand the nature and regulation of the genes on the X and Y chromosomes of mammals and their potential relationship to the biology of aging. Insights are expected to be gained on the nature of the aging process and the role of the sex chromosomes in that process, and whether there is any genetic basis for the observation that males, from fetus to adult, generally have a greater frequency of mortality than females.

BACKGROUND

Recent advances in the use of molecular genetics techniques for mapping, cloning and sequencing of genes on the mammalian sex chromosomes (the X and Y chromosomes in humans) are providing insight into the functional roles of such chromosomes. It is possible that such functions are related to the biological process of aging.

Numerous genes have been located and studied on the human X chromosome. Furthermore, specific inactivation of one of the two X chromosomes in each

female cell occurs early in fetal development; apparently this serves as a dosage compensation mechanism, to avoid the deleterious effects seen with excess X-chromosome expression. Recent evidence in rodents suggests that at least some genes on these Lyonized chromosomes are reactivated in aged animals. Also of interest is the recent finding that the active site subunit of human DNA polymerase alpha, the major DNA polymerase required for DNA replication and cell proliferation, is located on the X chromosome.

However, it is not known whether genes for DNA polymerase or other X-coded proteins are re-activated during aging. Nor is it known whether late-onset reactivation of inactive X-chromosomes is a protective mechanism for females, thus contributing to their relative longevity.

Some genes coding for proteins involved in the immune response are known to be located on the x-chromosome. Furthermore, auto-immune diseases are more prevalent in women than in men, especially in later life. Thus, it is possible that the decline in immune function is delayed in females and contributes to the longevity differential.

While functional genes on the Y chromosome are yet to be demonstrated, there appear to be Y-specific determinants of biological development, such as the testicular determining factor region. Furthermore, a large family has been found recently with an increased lifespan for males who carry a major deletion of Y DNA.

It is certainly clear that among humans in modern societies males have a higher frequency of mortality (from fetus to adult) than females. Consequently, the ratio of males to females is about 1.15 among early human fetuses, dropping to 1.06 at birth, and falling to 1.0 by age thirty in the Caucasian population. Heart disease, lung cancer, alcoholism, and accidents or violence are major factors in the higher mortality of males versus females. Thus, the mean life expectancy at birth in industrialized societies is about 78 years for females and 71 years for males, leading to a predominance of females among older persons (the ratio of males to females is predicted to fall, to 0.7 among persons over age 65 and to 0.4 among those over age 85 by the Twenty-first Century).

However, it is not known whether, in addition to known hormonal, environmental, and social/behavioral influences, there is a more fundamental genetic difference between men and women which influences longevity.

GOALS AND SCOPE

The goal of this announcement is to encourage research on the genes of the mammalian sex chromosomes, to determine what genes and control functions are present and which of them may be related to the process of biological aging. The new techniques of genetics and molecular biology make possible the isolation, sequencing and mapping of X and Y genes; they provide an opportunity to determine the functions of such genes; and they provide ways to examine the possible relationship of such genes to the causes of biological aging. Such an understanding may provide insights into the fundamental nature of aging, and into the basis for the observation that men at all ages, from fetus to adult, have a shorter life expectancy than women.

SPECIFIC OBJECTIVES

Research and training grant applications are sought to test hypotheses and to elucidate fundamental mechanisms of aging, using genetic and molecular biological techniques in the study of the sex chromosomes of mammals, including humans. Research is encouraged in, but not limited to, the following areas:

1. Identify the genes on the X and Y chromosomes of mammals or human beings, to map and sequence such genes, and to study their possible relationship to the aging process.
2. Characterize the products encoded by the genes of the sex chromosomes, and determine their potential role in aging.
3. Determine whether the subunits of the several known mammalian DNA polymerases are encoded by DNA on the X chromosome, and how their expression and function is controlled.
4. Define how extensive is the age-related reactivation of inactive X chromosomes, in rodents and in other mammalian and human cells.
5. Determine whether immune function and its decline with age contribute to the gender gap in longevity.

6. Determine whether genes on the X or Y chromosomes are responsible for some fraction of the greater life expectancy of females over males in society.

MECHANISMS OF RESEARCH AND RESEARCH TRAINING SUPPORT

The primary mechanisms for support of this program are:

1. Research project grant.
2. Postdoctoral fellowship.

Additional mechanisms for support are:

1. First Independent Research Support and Transition Award, for newly independent investigators; support ceiling of \$350,000 over five years.
2. Physician Scientist Award, for clinically-trained investigators; support ceiling of \$40,000 per year for salary and up to \$20,000 per year for supplies, for a five year period.
3. Research Career Development Award; up to \$40,000 per year for salary, for five years.
4. Institutional Training Grant, from NIA or as a supplemental position to those from other Institutes, for aging-related research.

Applicants are encouraged to contact NIA or NICHD Staff for information and advice regarding submission of proposals under this announcement.

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 review, and to the appropriate Institute or Division of NIH for final review by its National Advisory Council or Board. Applications submitted in response to this program announcement will compete with all grant applications for funding consideration; there is no specific set-aside funding for these applications.

METHOD OF APPLYING

Use the appropriate NIH research or research training grant application kit. If your institution does not have them, copies may be obtained by calling (NIH phone 301-496-7441) or by writing:

Office of Grant Inquiries
Division of Research Grants
National Institutes of Health
Westwood Building Room 449
5333 Westbard Avenue
Bethesda, Maryland 20892

Please type the phrase, "NIA/NICHD Genetics Program Announcement" on the face page, line 2, of the application, and enclose a cover letter indicating that the application is in response to this NIA/NICHD announcement. Forward the original and six (6) copies of the application to:

Division of Research Grants
National Institutes of Health
Westwood Building Room 449
Bethesda, Maryland 20892**

Applicants are encouraged to send a one-page letter of intent to the appropriate NIA or NICHD Genetics or Molecular Biology Program at the address indicated below. Please include the name of the principal investigator, institutional address, title of application, and a descriptive title of the application. A letter of intent is not binding, is not a requirement for consideration, and does not enter into the review of a subsequent application.

For projects proposing to study the genetic influence of sex chromosomes in biological aging and longevity, please contact:

Dr. Alan R. Price, Genetics Program Administrator, or
Dr. Huber R. Warner, Molecular Biology Program Administrator
Molecular and Cell Biology Branch
Building 31, Room 5C19
National Institute on Aging
National Institutes of Health
Bethesda, Maryland 20892
Telephone: (301) 496-6402

For projects proposing to study the genetic involvement of the sex chromosomes in sex differentiation, gonadal development, or disorders thereof, please contact:

Dr. Michael E. McClure
Head, Reproductive Genetics and
Immunology Program
Reproductive Sciences Branch
Center for Population Research
Landow Building, Room 7633
National Institute of Child Health
and Human Development
National Institutes of Health
Bethesda, Maryland 20892
Telephone: (301) 496-6515

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

5333 Westbard Avenue
Bethesda, Maryland 20816