NIH GUIDE

For Grants and Contracts

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The NIH Guide announces scientific initiatives and provides policy and administrative information to individuals and organizations who need to be kept informed of opportunities, requirements, and changes in extramural programs administered by the National Institutes of Health.

Vol. 16, No. 42
December 25, 1987

Vol. 16, No. 42, December 25, 1987

NOTICE

DATED ANNOUNCEMENTS (RFPs AND RFAs AVAILABLE)

ONGOING PROGRAM ANNOUNCEMENTS

NOTICE

NOTICE OF MEETING - THE HEALTH OF BIOMEDICAL RESEARCH INSTITUTIONS

P.T. 42; K.W. 1014002, 0710030

National Institutes of Health

Notice is hereby given that the National Institutes of Health (NIH) will hold the fifth and sixth meetings of a series of seven regional public briefing meetings to be conducted under the auspices of the Advisory Committee to the Director, NIH, on "The Health of Biomedical Research Institutions." The purpose of the meetings is two-fold:

1 to provide current information concerning the activities of the NIH by describing the broad political context in which the NIH operates, discussing the Federal budget process as it affects the formulation of the NIH budget, demonstrating recent trends in the funding of NIH programs, discussing the broad strategies adopted by NIH to meet emerging needs, and describing new NIH policies and programs designed to achieve program objectives; and

2 to solicit through public testimony the views of biomedical researchers, university faculty and administrators, representatives of professional societies, and other interested parties concerning the impact of the Federal system of sponsored research on the health of biomedical research institutions.

The fifth meeting will be held on Thursday, February 18, 1988 from 9:00 a.m. to 4:30 p.m. at the University of Texas Southwestern Medical Center at Dallas, Dallas, Texas. The sixth will be held on February 19, 1988 from 9:00 a.m. to 4:30 p.m. at the Emory University School of Medicine, Atlanta, Georgia. Notice of the time and location of the final meeting will be published later.

Following a presentation by the Director, NIH, a panel comprised of members of the Advisory Committee to the Director, NIH, representatives of NIH national advisory councils, institute directors, and other senior NIH staff will spend the remainder of the day receiving testimony from public witnesses. Each witness will be limited to a maximum of ten minutes. Attendance and the number of presentations will be limited to the time and space available. Consequently, all individuals wishing to attend or to present a statement at this public meeting should notify, in writing:

Jay Moskowitz, Ph.D.
Executive Secretary, Advisory Committee to the Director
National Institutes of Health
Shannon Building, Room 137
Bethesda, Maryland 20892
Telephone: (301) 496-3152

Those planning to make a presentation should file a one-page summary of their remarks with Dr. Moskowitz by January 22, 1988; a copy of the full text of these remarks should be submitted for the record at the time of the meeting. Please indicate which of the two meetings you plan to attend. Additional information may be obtained by calling:

Mr. Edward Lynch
Division of Program Analysis
Office of Program Planning and Evaluation
National Institutes of Health
Shannon Building, Room 233
Bethesda, Maryland 20892
Telephone: (301) 496-4418

TOXICOLOGY OF POTENTIAL ANTICONVULSANT DRUGS

RFP AVAILABLE: NIH-NINCDS-88-05

P.T. 34; K.W. 0740010, 1007009

National Institute of Neurological and Communicative Disorders and Stroke

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) has a requirement for continuing the evaluation of the toxicology of potential anticonvulsant drugs in rats, dogs or monkeys.

The Epilepsy Branch, Division of Convulsive, Developmental, and Neuromuscular Disorders of the National Institute of Neurological and Communicative Disorders and Stroke conducts an extensive Antiepileptic Drug Development (ADD) Program aimed at identifying potentially new antiepileptic agents to be used in man. This program employs a stepwise approach utilizing a systematic series of screening tests and decision steps to advance candidate compounds through the stages of preclinical and clinical development. Those compounds which demonstrate therapeutic indices are advanced to subchronic oral toxicity studies in either rat, dog, or monkey. This toxicity project provides the necessary safety information from acute and chronic studies in animal species required by the FDA.

The Contractor will be responsible for performing dose-range finding studies and fully audited GLP subchronic studies lasting either 30 days or 13 weeks. The dose-range finding studies will consist of hematology, clinical chemistry, necropsy, and tissue collection. Microscopic examination of fixed tissue will be done when warranted by the data. The Good Laboratory Practices (GLP) subchronic studies will consist of three dosing groups and a vehicle control. Hematological and clinical chemistry parameters, urinalysis and ophthalogical examinations shall be performed. Microscopic examination of tissues collected from all animals in the study will be carried out.

Prospective offerors are advised that this requirement represents a recompetition of work currently being performed under NINCDS Contract No. NO1-NS-3-2358 with Hazleton Laboratories America, Inc.

The Government anticipates one contract award for a performance period of five (5) years.

RFP NIH-NINCDS-88-05 will be available on December 31, 1987. Responses will be due by March 1, 1988.

To receive a copy of the RFP, please supply this office with two (2) self-addressed mailing labels. Requests must cite the RFP number referenced above. All responsible sources may submit a proposal which will be considered by the agency. The RFP package will be available upon request to:

Contracting Officer, Contracts Management Branch, NINCDS,
National Institutes of Health
Federal Building, Room 901
7550 Wisconsin Avenue
Bethesda, Maryland 20892

STUDIES OF THE ELECTROCHEMISTRY OF STIMULATING ELECTRODES

RFP AVAILABLE: NIH-NINCDS-88-02

P.T. 34; K.W. 0740050, 0710050

National Institute of Neurological and Communicative Disorders and Stroke

The National Institute of Neurological and Communicative Disorders and Stroke has a requirement to develop materials for use in neural stimulating electrodes, to evaluate the electrochemical processes that occur at the electrode-electrolyte interface during pulsing regimens characteristic of neural prosthetic applications, and to apply these findings to the fabrication of prototype neural stimulating electrodes.

Offerors must have experience in the electrochemistry of electron conducting electrodes and charge injection into ionic electrolytes.

This requirement represents the recompetition of a current contract with EIC Laboratories, Inc., and the incumbent is expected to reapply.

This is an announcement of an anticipated Request for Proposals. RFP-NIH-NINCDS-88-02 will be issued on or about December 28, 1987, with a closing date for receipt of proposals set for February 29, 1988.

To receive a copy of the RFP, please supply this office with two self-addressed mailing labels. All responsible sources may submit a proposal which will be considered by the agency. The RFP package will be available upon request to:

Contracting Officer, Contracts Management Branch, NINCDS
National Institutes of Health
Federal Building, Room 901
7550 Wisconsin Avenue
Bethesda, Maryland 20892

NATIONAL COLLABORATIVE DIAGNOSTIC IMAGING TRIAL PROJECTS

RFA AVAILABLE: 88-CA-02

P.T. 34; K.W. 0706030, 0755015, 0715035

National Cancer Institute

Application Receipt Date: March 11, 1988

The Division of Cancer Treatment (DCT) of the National Cancer Institute (NCI) invites applications for cooperative agreements for participation in the National Collaborative Diagnostic Imaging Trial Projects. The objectives of the present proposal are to conceive new approaches for the development and implementation of national cooperative trials carried out by multiple institutions using this approach to develop new algorithms for the appropriate sequential use of the most advanced imaging procedures to diagnose, stage and monitor malignant disease.

The decades of the 1970s and 1980s have been characterized by spectacular technical advances in medical imaging, particularly those applied to tumor definition and characterization. These technologies have now developed to the stage where a clear identification of the relative roles of each diagnostic modality in the diagnosis and staging of cancer is warranted. To date, most comparative studies evaluating imaging technologies have been based at a single institution and have involved small numbers of cases making their results often equivocal and not applicable in large-scale patient care settings.

Diagnostic Imaging procedures cost in excess of ten billion dollars annually, representing approximately 3 percent of the total health care monies expended in the United States. It is also claimed that nearly 30 percent of these imaging studies are inappropriately applied or unnecessary. In 1983, in excess of two billion dollars was expended in capital equipment acquisition in the diagnostic field, not including supplies, service or replacement parts. (Source: Hambrecht and Quist estimates, Diagnostic Imaging (Nov. 1984.)

A multi-institutional collaborative clinical trials group was funded in 1987 by NCI to assess the relative role of each imaging modality in cancer management of carcinomas of the prostate and lung.

The objective of this RFA is to support multicenter cooperative clinical trials to determine the most effective imaging procedures required to stage and monitor pancreas and colorectal carcinomas. The successful applicants will join the on-going collaborating institutions already funded by NCI as the Radiologic Diagnostic Oncology Group (RDOG); (86-CA-10).

It is anticipated that approximately eight to ten scientifically meritorious applications can be funded.

The label available with the 9/86 revision of application 398 must be affixed to the bottom of the face page. Failure to use this label could result in delayed processing of your application such that it may not reach the review committee in time for review.

Request for copies of the complete RFA should be addressed to:

Dr. Matti Al-Aish, Deputy Chief
Diagnostic Imaging Research Branch
Radiation Research Program
National Cancer Institute
National Institutes of Health
Landow Building, Room 8C09
Bethesda, Maryland 20892
Telephone: (301) 496-9531

CYSTIC FIBROSIS RESEARCH CENTERS

RFA AVAILABLE: 88-DK-07

P.T. 04; K.W. 0755030, 0765035, 0415000, 0715165, 0790005, 1002008, 1002019

National Institute of Diabetes and Digestive and Kidney Diseases
National Heart, Lung, and Blood Institute

Application Receipt Date: April 11, 1988

The Division of Diabetes, Endocrinology, and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Division of Lung Diseases of the National Heart, Lung, and Blood Institute (NHLBI) announce a national competition for awards to establish a limited number of Cystic Fibrosis Research Centers for the purpose of investigating the etiology, pathophysiology, and treatment of cystic fibrosis.

BACKGROUND

Cystic fibrosis (CF) is the most common lethal genetic disorder in the Caucasian population. It is inherited as an autosomal recessive trait and many patients die within the first two decades of life. The clinical syndrome appears as a generalized dysfunction of exocrine glands or epithelial surfaces and is characterized by elevated sweat electrolytes, secretion of highly viscous mucus, pulmonary infections, and progressive loss of function in the lungs, pancreas, liver, intestines, and other organs.

The CF gene has been localized to within 300,000 DNA base pairs of a gene-linkage marker on the long arm of chromosome 7. Research efforts are now focused on identifying the CF gene and the protein which it encodes. It is hoped that isolation of the defective gene responsible for cystic fibrosis will elucidate the underlying biochemical defect(s). It is also hoped that identification of the CF gene will lead to methods of identifying its asymptomatic carriers and ultimately to a neonatal screening technique for the general population. Research in CF has led to the hypothesis that a diminished negative ion permeability in the distal sweat duct underlies the elevated sweat concentrations of sodium chloride considered diagnostic for the disease. It is now therefore postulated that in normal cells chloride follows sodium passively via a chloride/bicarbonate exchange or by a chloride ion channel. In CF, this antiport/channel or its regulation is defective, resulting in sodium only being partially reabsorbed, resulting in high sodium ion and chloride ion and low biocarbonate ion in the sweat duct lumen. Recent results suggest that the problem in cystic fibrosis relates not to the presence or absence of the chloride ion conductance but to the regulation of this conductance by a cyclic AMP dependent process.

These rapid advances were made possible by application of new state-of-the-art techniques of molecular and cell biology to the study of CF. With support through Cystic Fibrosis Research Centers, scientists can pursue exciting current opportunities to advance fundamental understanding of the pathogenesis of CF and, ultimately, therapy of the disease.

RESEARCH GOALS AND SCOPE

The overall goal of a Cystic Fibrosis Research Center is to stimulate a multidisciplinary approach aimed at promoting advances in basic science research on the cellular and molecular mechanisms underlying cystic fibrosis and the integration and application of this knowledge to clinical investigations. CF Centers should have a central theme to which all constituent projects relate and which serves as an integrating force to achieve an overall common goal. Emphasis in proposed projects should be on the exploration of basic mechanisms underlying CF, the elaboration of new and significant hypotheses, and the generation of novel strategies for approaching current clinical and fundamental issues.

The scope of research that could meet the goals of the CF Center program includes: 1) identification, cloning, and characterization of the CF gene and its protein product, 2) DNA sequence analysis of the cloned gene for generation of synthetic peptide antibodies valuable for biochemical studies characterizing the protein product, 3) studies aimed at defining etiological factors and pathogenetic mechanism, 4) investigations into the relationship between the genetic defect(s) and the resulting pathophysiology, 5) development of other reliable phenotypic markers characteristic of CF cells in culture, besides that of the currently available chloride impermeability, 6) studies focused on biochemical and molecular aspects of the regulation of epithelial ion transport in epithelial cells such as characterization of the intermediates involved in chloride channel regulation, 7) development and evaluation of new and/or improved therapeutic approaches effective in alleviating the clinical symptoms of the disease, 8) evaluation of gene replacement therapy or antisense RNA as possible prevention modalities, 9) development of diagnostic tests useful for carrier assessment and prenatal screening, 10) development of improved conditions for routinely growing and passaging CF cells and development of immortalized CF cell lines, facilitating studies presently hampered by a scarcity of cells, and 11) evaluation of the factor(s) contributing to chronic respiratory infections, usually by Pseudomonas.

Although the overall objective of the CF Center program is the same for both of the sponsoring institutes, the underlying framework by which this goal can be achieved varies somewhat between the two institutes, as does the scope of some of the studies.

NIDDK

The National Institute of Diabetes and Digestive and Kidney Diseases supports research on the etiology, pathophysiology, and treatment of CF as a whole. The key elements of NIDDK's CF Center program include: (1) basic an dclinical research projects; (2) research cores, providing shared resources such as techniques, instruments, tissues, patient populations, and research seminars; and (3) pilot and feasibility studies.

NHLBI

The National Heart, Lung, and Blood Institute supports research on the etiology, pathophysiology, and treatment of CF, specifically as it relates to pulmonary manifestations. The NHLBI's CF Centers program consists of three main components: basic research, clinical research, and core unit(s) designed to support the major scientific component(s). Pilot or feasibility studies, if they are included in the application, must be incorporated within research projects.

MECHANISM OF SUPPORT

Support for this program will be through a center grant. Successful applicants will direct and carry out the center's research projects. However, any substantive modifications in that program must be mutually agreed on by the center director, the grantee institution, and the appropriate sponsoring institute (NIDDK or NHLBI). Applications received in response to this Centers announcement will be considered for assignment to both the NIDDK and NHLBI, applying current referral guidelines. It is anticipated that NIDDK will support two or three centers and NHLBI will support one center at a level not to exceed $800,000 per year per Center, including indirect costs. These awards will be made for five years and the progress of each Center will be evaluated annually.

APPLICATION AND REVIEW PROCEDURES

The applications for centers solicited in this announcement will be evaluated in national competition by a special review committee. Deadline for the receipt of the applications will be April 11, 1988. Prospective applicants are encouraged to submit a letter of intent by March 1, 1988. Applications deemed by Institute staff not to meet the published guidelines will be judged unacceptable and will be returned to the applicant.

Applications must be submitted on PHS Form 398 (Rev. 9/86). The title "CYSTIC FIBROSIS RESEARCH CENTERS" and RFA number 88-DK-07 should be typed in item 2 on the face page of the application. The original and four copies of the application should be sent or delivered to:

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

Two additional copies of the application should be sent to:

Dr. Anthony Demsey
Chief, Review Branch, NIDDK
Westwood Building, Room 604
Bethesda, Maryland 20892**

INQUIRIES

Potential applicants must request CF Center Guidelines from:

Nancy Lamontagne, Ph.D.
Cystic Fibrosis Program Director
NIDDK, NIH
Westwood Building, Room 607
Bethesda, Maryland 20892**
Telephone: (301) 496-4980

Susan P. Banks-Schlegel, Ph.D.
Airways Diseases Branch
NHLBI, NIH
Westwood Building, Room 6A15
Bethesda, Maryland 20892**
Telephone: (301) 496-7332

This program is described in the Catalog of Federal Domestic Assistance, No. 13.838. Grants will be awarded 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 intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

STATE HUMAN RESOURCE DEVELOPMENT PROGRAM

P.T. 14; K.W. 0780000

National Institute of Mental Health

Application Receipt Date: February 12, 1988

The National Institute of Mental Health (NIMH) announces the State Human Resource Development (SHRD) Program, MH-87-23, which awards grants to enhance the capacity of State mental health agencies to improve mental health services by supporting human resource development in the State. Only State departments of mental health are eligible to apply under this program. Three types of projects are eligible for support: Capacity Building, Special, and Academic Linkages. It is expected that approximately $800,000 will be available for this program in fiscal year 1988. The maximum level of support for a SHRD Capacity Building project is $75,000 per year; for Special projects, $100,000 per year; and for Academic Linkage projects, $30,000 per year. NIMH will accept applications for grants under the single receipt date of February 12, 1988. Potential applicants interested in obtaining further information should contact:

Vernon R. James, Ed.D.
Chief, State Planning and Human Resource Development Branch
Division of Education and Service Systems Liaison, NIMH
Parklawn Building, Room 7-103
5600 Fishers Lane
Rockville, Maryland 20857
Telephone: (301) 443-4257

CLINICAL TRAINING GRANTS FOR SUPPORT OF RACIAL/ETHNIC MINORITY AND DISADVANTAGED STUDENTS

P.T. 44, BB, FF; K.W. 0720005, 0785185, 0785130, 0414004, 0730050

National Institute of Mental Health

The National Institute of Mental Health (NIMH) invites new and competing renewal applications for clinical training programs whose purpose is to recruit and train racial/ethnic minority and disadvantaged individuals as mental health professionals in social work, psychiatric nursing, psychiatry, and psychology for practice with persons with serious mental disorders. In fiscal year 1988, it is expected that approximately $500 thousand to $1 million will become available for new and competing awards under this request for applications. It is expected that clinical training grant awards will range in size up to the maximum of $80,000 per year for direct costs. Approximately 6 to 14 awards are expected to be made. Support may be requested for up to 3 years. Since NIMH can make no commitment beyond the first year, the objectives and activities of the first year should be designed to be significant in themselves. NIMH will accept applications for clinical

training grants in this area under the single receipt date of February 12, 1988. Applicants must use the Public Health Service application kit (PHS 398, Rev. 9/86). Staff consultation on clinical training grants is available from the following:

Psychiatric Nursing -
Dr. Jeannette G. Chamberlain
Chief, Psychiatric Nursing Education Program
Room 7C-06
Telephone: (301) 443-5850

Psychiatry -
Dr. Melvyn R. Haas
Chief, Psychiatry Education Program
Room 7C-10
Telephone: (301) 443-2120

Psychology -
Dr. Paul Wohlford
Chief, Psychology Education Program
Room 7C-06
Telephone: (301) 443-5850

Social Work -
Dr. Neilson F. Smith
Chief, Social Work Education Program
Room 7C-06
Telephone: (301) 443-5850

The mailing address for all of the above is:

Division of Education and Service Systems Liaison
National Institute of Mental Health
Parklawn Building, 5600 Fishers Lane
Rockville, Maryland 20857

ONGOING PROGRAM ANNOUNCEMENTS

THE ROLE OF GROWTH REGULATORY FACTORS IN NORMAL AND NEOPLASTIC PROSTATE

P.T. 34; K.W. 0760020, 0765015, 0715035

National Cancer Institute

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

The Organ Systems Program of the Division of Cancer Prevention and Control, National Cancer Institute, seeks applications for studies to identify and characterize growth regulatory factors produced by normal or neoplastic prostate cells, to determine their possible autocrine or paracrine functions in normal growth and neoplasia, and to define the role of growth regulatory factors in the pathogenesis and metastatic spread of prostate cancer.

BACKGROUND

The prostate displays a wide range and diversity for growth and metastatic potential. Prostate cancer is associated with an unusual and extremely high prevalence of latent or dormant cancer that is clearly identified on pathological examination, but which in most cases will never grow further to become clinically manifest. For unknown reasons growth is held in check in 90% of these latent prostate cancers and this is by totally unknown biological mechanisms. However, those latent cancers that are subsequently activated to grow, produce a mortality rate that makes prostate cancer the second leading cause of cancer deaths in the U.S. male.

The responsiveness of prostate tissue to androgens and the role of androgens in prostatic cancer makes the prostate amenable to studying a putative role for growth factors in mediating androgen action. In the absence of androgen, prostate cancer does not develop. For example, there are no reported cases of prostate cancer in individuals who have been castrated in early life. In advanced cases of prostate cancer, removal of androgens by castration or estradiol treatment results in a marked regression of the cancer. However, such regression is usually transitory and in the majority of cases there is a recurrence of cancerous growth at some time after endocrine ablation therapy. Thus, prostate cancer appears androgen dependent during the early stages of oncogenesis.

It is clear that the initial stimulation of prostate growth is mediated by androgenic steroids. It may be that under androgen regulation, growth factors are expressed at specific periods of development, thereby playing an important role in prostate growth and/or differentiation. Indeed, evidence suggests that growth factors, stimulated by estrogens in estrogen responsive cells, may serve as autocrine mediators of estrogen action. There is also evidence that differentiation of epithelial cells within the prostate is mediated by paracrine signals from stromal cells. Thus, it is reasonable to study growth factors in the prostate which may serve as paracrine and/or autocrine mediators of androgen stimulation.

A characteristic property of the prostate is that it contains a high concentration of androgen receptors. Androgen receptors exhibit a high affinity and specificity for androgenic steroids and these steroid receptor complexes bind to DNA in androgen-responsive genes. Recently the genes coding for two intranuclear steroid receptors, i.e., glucocorticoid and estrogen, have been cloned and sequenced. Interestingly, both have segments of nucleotide sequences very similar to a segment of the oncogene, vErb A, which codes for a nuclear protein. Other oncogenic products have been demonstrated to have sequence homologies similar to proteins that are important mediators of hormone action on target cells. It is therefore likely that growth factors within the prostate may be related to oncogene products. There is also the possibility that androgen-dependent cells within the prostate are transformed to an androgen-independent state by alterations in growth factor regulation. Thus, studies on growth factors in the prostate may elucidate alternative mechanisms by which androgens regulate prostate function and may contribute to understanding how cancer cells become androgen-independent.

As prostate growth regulatory factors are identified and purified, it becomes important to characterize the mechanisms by which they effect normal and malignant growth and their interactions with the different cellular elements of the prostate. Stromal elements can effect the growth of prostatic cancer cells. It has been reported that conditioned media from fibroblasts derived from the prostate, but not from the skin, contain a substance which inhibits the growth of an established prostatic cancer line in vitro. Defining the specificity of the stromal epithelial interaction of these paracrine factors may provide a better understanding of the wide variability of the malignant potential of prostatic cancer. Identification and purification of these paracrine factors could also open new avenues for treatment of prostatic cancer.

There are little data regarding autocrine factors involved in the growth of prostatic cancer. A prostatic epithelial cell growth medium has been formulated that contains cholera toxin, extract from either the pituitary or hypothalamus and epidermal growth factor. It is not known how these are related to endogenous endocrine, paracrine or autocrine factors that affect prostatic growth. Furthermore, these prostatic growth media are supplemented with glucocorticoids but not androgens. The lack of androgen effect on growth in vitro in contrast to in vivo is puzzling. The question is raised whether androgens block growth inhibitory factors in vivo, or whether cholera toxin, brain extract, and EGF provide growth stimulation that would otherwise be induced by androgens. The development of a spectrum of androgen-dependent prostatic cancer cell lines would permit resolution of which autocrine factors are important in the progression of prostatic cancer from androgen-dependent to independent growth.

Prostate cancer is a slow-growing solid tumor. Since there is little evidence of increased mitotic activity in prostate cancer compared to normal tissue, it has been suggested that prostate tumor growth regulation may possibly involve alterations in the tumor cell death rate, i.e., increased neoplastic growth reflects a shift in the balance between cell replication and the rate of cell death, such that a positive net accumulation of tumor cells occurs. To date, most investigations have focused on factors associated with increasing cell proliferation. Recently, it has been shown that androgen-sensitive tumor growth in rats is mediated through androgens decreasing the rate of tumor cell death, while in other tumor models, androgens have been shown to increase cell replication. How growth regulatory factors might alter the balance between cell proliferation and death by either a positive increase in cell replication or through altering or inhibiting the rate of cell death is not known.

RESEARCH GOALS AND SCOPE

Observations described above suggest that autocrine, paracrine and endocrine factors are involved with the regulation of prostate growth. It is timely to encourage research efforts to understand how normal prostate growth is controlled and regulated, and how these controls are altered or uncoupled in both androgen-sensitive and androgen-insensitive autonomous prostate cancer

growth and metastasis. This announcement is intended to stimulate research on prostate growth regulatory factors and address factors involved with stimulating DNA replication, and altering rates of cell death.

Possible approaches could include isolation and identification of prostate growth regulating factor(s) (stimulators and/or inhibitors) from normal and neoplastic prostate. Development of new animal and human prostate stromal and/or epithelial assay systems is encouraged since growth factor effects on different cell types may vary and such assay systems are essential for the identification of prostate specific factors. Growth regulatory factors need to be characterized in comparison to the biological activities of other known growth factors and purified for partial sequencing and production of polyclonal or monoclonal antibodies. Further structural analysis by isolation of cDNA probes from animal and human prostate cDNA libraries is encouraged. Obtaining the full nucleotide sequence of prostate growth regulatory factor(s) will make it possible to derive the amino acid sequence for comparison with sequences of known growth factors and oncogenes.

Biological activity of growth factors in the prostate could be pursued by identifying the cell types responding to growth regulatory factors, whether stromal or epithelial, by identifying specific cell surface receptors and by measuring the growth responses of different prostate cell types. Other possible approaches include localizing the site of production of prostate derived growth factors, determining the patterns of hormonal regulation of these factors and investigating their role as hormones. It has long been recognized that prostate development and growth are regulated by the male hormone, dihydrotestosterone. It is becoming increasingly suspect, however, that this effect of androgen is not a direct action on DNA synthesis, but rather one mediated by other intracellular regulators. From what is known about cell cycle control, it is likely that growth regulatory factors mediate androgen control of prostate growth. Thus, it will be important not only to determine whether growth factors are responsive to androgen stimulation of normal and neoplastic prostate, but to learn also whether other hormones and growth factors stimulate prostate growth regulatory factors.

The above describes examples of possible approaches. It is not implied that any single applicant should pursue all or any of these approaches. Other approaches with appropriate rationales are also encouraged.

MECHANISM OF SUPPORT

This program will be supported through traditional research grants. Policies for grant programs of the National Institutes of Health will apply.

APPLICATION AND REVIEW PROCEDURES

Grant applications in response to this announcement will be reviewed in accordance with the usual Public Health Service Peer Review (Study Section) procedures. Review criteria include the significance and originality of research goals and approaches; feasibility of research and adequacy of experimental design; adequacy of available facilities and appropriateness of the requested budget relative to the work proposed. Following Study Section review, further evaluation will be provided by an appropriate National Advisory Board/Council. Funding decisions will be based on the above evaluations and on the availability of funds.

Applications should be submitted on Form PHS-398, revised 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 an indefinite basis:

February 1 June 1 October 1

The phrase "Prostate Growth Regulatory Factors" should be typed on line 2 of the face page of the application. The original and six copies should be sent to:

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

A copy of the face page and summary page of the application should be sent under separate cover to:

Dr. Andrew Chiarodo
Organ Systems Section
Cancer Centers Branch
Division of Cancer Prevention and Control
National Cancer Institute
Blair Building, Room 717
Bethesda, Maryland 20892-4200
Telephone: (301) 427-8818

This program is described in the Catalog of Federal Domestic Assistance No. 13.393, Cancer Prevention Research. Awards will be made under authorization of the Public Health Service Act, Title III, 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 the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

EVALUATION AND UTILIZATION OF TRANSGENIC ANIMAL MODELS IN STUDIES OF PANCREATIC CANCER

P.T. 34; K.W. 0715035, 0755020

National Cancer Institute

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

The Organ Systems Program, through the National Cancer Institute Division of Cancer Prevention and Control, seeks applications proposing studies to evaluate, develop and utilize transgenic animal model systems for analyzing pancreatic cancer. The goal is to stimulate research in (1) the utilization of available transgenic mouse models of acinar cell pancreatic cancer for studies of mechanisms of carcinogenesis, cell of origin and tumor markers; (2) the establishment and use of transgenic murine model for studies of ductal cell pancreatic cancer; and (3) the establishment and use of transgenic systems in species other than the mouse, chiefly those which have a propensity for ductal cell pancreatic adenocarcinoma such as the Syrian hamster.

BACKGROUND

Pancreatic adenocarcinoma ranks as the fourth highest cause of cancer deaths in the United States. Of approximately 25,000 new cases in 1987, most will die within a year, and fewer than 500 are expected to live beyond five years. Current treatment methodologies are expected to have little effect on this outcome, and the causes and natural history of the disease are little understood. Additional studies of pancreatic adenocarcinoma are needed in order to develop markers for use in early detection, identify mechanisms of carcinogenesis, identify developmental time points in the malignant transformation process, and identify agents which may lead to prevention or control.

There are a number of reasons to believe that research in pancreatic cancer would be enhanced if additional useful animal tumor models were developed. Few investigators are using the tumor models which are currently available for studies of pancreatic carcinogenesis. One objection to most existing models is that they involve development of acinar cell adenocarcinomas rather than ductal tumors. Pathologists who study the human disease define it as ductal rather than acinar in appearance and possibly in origin. One model involving the injection of nitrosamines into Syrian hamsters does provide ductal cell tumors. Nevertheless, there is a long time to appearance of true adenocarcinomas, and there are differences among animals in time of appearance and nature of these lesions.

The recent development of transgenic mouse models for pancreatic cancer provides experimental systems which are accessible and manipulable. An accelerated production of transgenic models, using the mouse and additional species, would stimulate the field by providing tools for analyzing how oncogenes or transforming genes function in pancreatic tumorigenesis. Transgenic systems might allow delineation of stages when differentiating pancreatic cells become susceptible to initiation or promotion in carcinogenesis. Also, such systems might make possible the identification of environmental factors influencing these processes.

An issue which is related to the above considerations is that of identifying the cells of origin for pancreatic tumors. Are acinar and ductal cells of the pancreas both derived from common precursor stem cells? Concomitantly, are differences between acinar and ductal cells quantitative or qualitative? There is the possibility that ductal cell adenocarcinomas are derived from acinar cells which have de-differentiated as part of the transformation process. Some in vitro studies are consistent with this possibility. For example, AR42J pancreas tumor cells do not appear differentiated, but exposure to dexamethasone induces expression of nearly all the exocrine pancreatic secretory proteins. Similarly, organ cultures of pancreatic rudiments obtained at a stage when phenotypic expression is not yet apparent can be induced to express differentiation end-products prematurely.

RESEARCH GOALS AND SCOPE

At the present time, origination of at least two transgenic mouse systems, both resulting in acinar cell pancreatic adenocarcinomas, has been reported. In the development of a transgenic system, expression of a foreign gene can be targeted to cells of the pancreas. A foreign gene is attached to the promoter-enhancer region of a pancreas-specific gene, such as that for pancreatic elastase. Insertion of such a DNA construct into the germ line by injection into a mouse egg results in subsequent expression of the gene in the pancreas cells.

Simian tumor virus 40 causes malignant transformation in a number of systems, and if used as the transforming portion of a construct, results in acinar cell pancreatic adenocarcinomas which develop in mice at about 3-6 months of age. Such newborn mice show hyperplasia of the pancreas, and there appears to be a 2-3 fold increase in the number of cells per acinus, with the overall morphology remaining fairly normal. At about one-month of age, the majority of these cells are tetraploid, when hundreds of nodules develop within the pancreas. The nodules proliferate rapidly and by 3-4 months of age give rise to a multi-nodular, 3-9 gm pancreas. At this time, individual nodules have different characteristic aneuploid DNA contents. Currently, four lines of transgenic mice carrying SV40 are available.

Introduction of pancreatic elastase-SV40 gene constructs into the germ line of mice have provided strains in which 100 percent of the progeny develop pancreatic cancer. Several strains are homozygous with regard to the genetic construct. They need to be evaluated for tumor histopathology and for features of tumor development. They might be useful in studies of mechanisms that bring about carcinogenesis and might be appropriate for use in studies of tumor markers for pancreatic cancer.

It might be possible to attach an oncogene to the promotor-enhancer region of a gene specific for pancreatic ductal cells, thereby targeting transformation event(s) specifically to ductal cells. Such a model would be highly useful in pancreatic cancer research. The feasibility of this approach is demonstrated by the current transgenic mouse models which target transformation to acinar cells. Similar to the SV40 transgenic system described above, introduction of oncogenic (mutated) ras-pancreatic elastase constructs will transform acinar cells. The fetuses develop acinar cell adenocarcinomas, and the mice die a few days after birth. By day 16 of embryogenesis, just a few days after the pancreas has begun to develop, the pancreas is already huge, perhaps 3-10 times normal size. The acinar structure is clearly abnormal, and by day 20, about the time of birth, the enlarged pancreas is very cystic, and normal acinar structure does not exist. This embryonic tumor model is potentially useful, but since the mice die before breeding age, a colony cannot be established.

In Syrian hamsters, chemical carcinogens induce primarily ductal cell tumors of the pancreas, where in other species the same carcinogens induce acinar cell tumors. This indicates that the development and resulting histopathology of such tumors is influenced by species-specific factors. The phenotypic appearance of transgenic adenocarcinomas might be similarly influenced by how introduced constructs interact with host species. If so, then studies of transgenic models might provide answers to questions about pancreatic tumor cell lineage and control of tumor cell differentiation.

Immediate obstacles to the development of additional transgenic pancreatic cancer models are largely operational, such as the availability and manipulability of sufficient numbers of rodent or hamster eggs. Researchers in cellular and molecular biology and in carcinogenesis, who have this capability and have expertise available for developing transgenic animal systems, would be appropriate applicants for this announcement. Also, multidisciplinary teams which have expertise in transgenic systems, molecular biology, reproductive biology and carcinogenesis would be appropriate applicants.

MECHANISM OF SUPPORT

This program will be supported through traditional research grants. Awards will be made to public, private non-profit, and for profit organizations. Policies for grant programs of the National Institutes of Health will apply.

APPLICATION AND REVIEW PROCEDURES

Grant applications in response to this announcement will be reviewed in accordance with the usual National Institutes of Health Service peer review (Study Section) procedures. Review criteria include the significance and originality of research goals and approaches; feasibility of research and adequacy of experimental design; adequacy of available facilities and appropriateness of the requested budget relative to the work proposed. Following Study Section review, further evaluation will be provided by an appropriate National Advisory Board/Council. Funding decisions will be based on the above evaluations and on the availability of funds.

Applications should be submitted on Form PHS-398, revised 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 an indefinite basis:

February 1 June 1 October 1

The phrase "EVALUATION AND UTILIZATION OF TRANSGENIC ANIMAL MODELS IN STUDIES OF PANCREATIC CANCER" should be typed on line 2 of the face page of the application. The original and six copies should be sent to:

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

A copy of the face page and summary page of the application should be sent under separate cover to:

Dr. William E. Straile
Organ Systems Section
Cancer Centers Branch
Division of Cancer Prevention and Control
National Cancer Institute
Blair Building, Room 717
Bethesda, Maryland 20892-4200
Telephone: (301) 427-8818

This program is described in the Catalog of Federal Domestic Assistance No. 13.393, Cancer Prevention Research. Awards will be made under authorization of the Public Health Service Act, Title III, 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 the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

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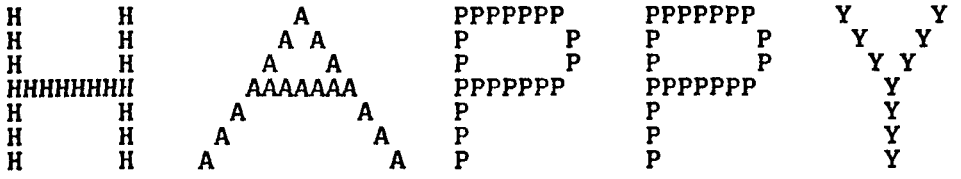

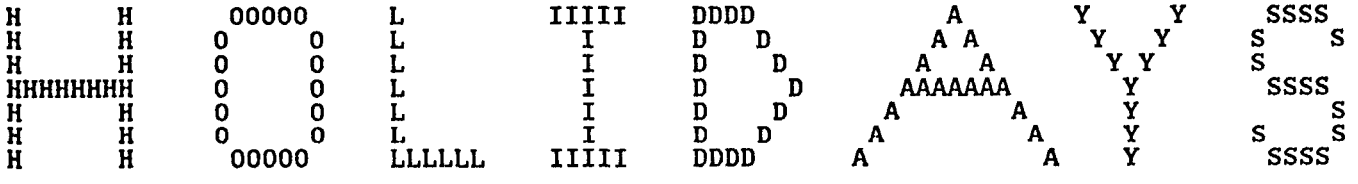

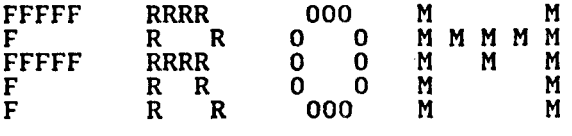

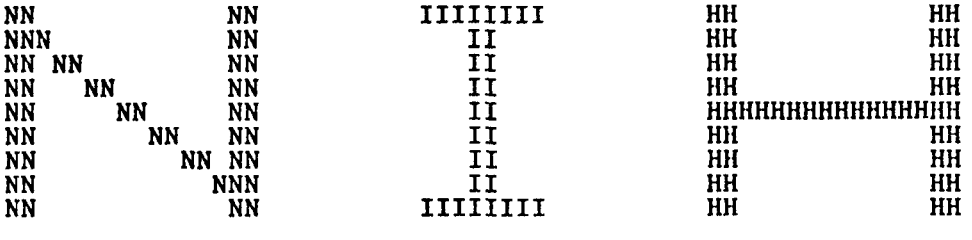

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