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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. 14 - APRIL 17, 1987

Vol. 16, No. 14, April 17, 1987

DATED ANNOUNCEMENTS (RFAs and RFPs AVAILABLE)

ONGOING PROGRAM ANNOUNCEMENTS

ERRATA

SYNTHESIS AND TESTING OF NON-STEROIDAL MALE CONTRACEPTIVE AGENTS

RFP AVAILABLE: NICHD-CD-87-4

P.T. 34; K.W. 0750020, 0755025, 1003006, 0710100

National Institute of Child Health and Human Development

The Contraceptive Development Branch, Center for Population Research, National Institute of Child Health and Human Development, has a requirement for the synthesis and testing of non-steroidal male contraceptive agents. The basic objectives of the project are the design, synthesis, and testing of non-steroidal agents which inhibit testicular sperm development, inhibit post-testicular sperm maturation and functions, and preferentially affect Sertoli cell function.

Organizations must have adequate facilities and capabilities to carry out the proposed synthetic chemical program. Specifically excluded from this project are LHRH analogs; gossypol derivatives; steroidal agents; all alkylating agents including chlorohydrin, deoxychlorosugars, nitrogen mustards, ethyleneimines, and sulfonoxyalkanes; nonspecific antimetabolites; antimitotic agents; N-substituted diamines (such as Win. 13,099); and nitroheterocyclic compounds. Proposals to merely collect compounds from various sources and/or only perform biological assays will not be considered.

RFP-NICHD-CD-87-4 will be issued on or about May 1, 1987. Proposals will be due approximately 60 days thereafter. Copies of the RFP may be obtained by sending written requests to the following address. Please enclose a self-addressed label.

Paul J. Duska, Contracting Officer
Contract Management Section, OGC
National Institute of Child Health and Human Development
Landow Building, Room 6C25
7910 Woodmont Avenue
Bethesda, Maryland 20892

MARKERS OF EXFOLIATED BLADDER CANCER CELLS CORRELATED WITH TUMOR PROGRESSION AND RECURRENCE

P.T. 34; K.W. 0715035, 0705075, 0755010, 0710070, 1002004

RFA AVAILABLE: 87-CA-23

National Cancer Institute

Application Receipt Date: July 15, 1987

The Division of Cancer Prevention and Control, through the Organ Systems Program, invites research grant applications from organizations which are capable of participating in a network of collaborating research laboratories charged with testing chemical and immunologic markers for urinary bladder cancer. Research will be conducted to determine a rationale for applying markers to distinguish specific populations of exfoliated bladder cells in cancer patients.

OBJECTIVE AND SCOPE

A major goal of this RFA is to stimulate the development of an inter-organizational, cell marker network for bladder cancer. The NCI proposes to initiate interaction among three to five cell marker laboratories, each with an image analysis, flow cytometry or slit-scan capacity. Scientists in the network would be encouraged to conduct collaborative research in the diagnosis and treatment or urinary bladder cancer. Members of the network would plan, complete and evaluate laboratory studies and patient protocol studies, and decisions would be made on logical steps to take in the research program. Thus, the investigators in the network would have full responsibility for planning and directing research.

Improvements are needed in coordinating cell marker research with the automated cytometry of exfoliated bladder cancer cells, and there is a need to develop new methods for cell marker identification and analysis. Additional aims are to: 1) text chemical and immunologic cell markers and determine their application in distinguishing populations of exfoliated bladder cancer cells; 2) extend the research base in exfoliative bladder cell marker technology, and apply the new findings in studies of bladder tumor progression and recurrence after diagnosis; 3) redefine the marker characteristics of exfoliated bladder cancer cells, and factor

the data into a tumor classification which is useful in patient management; and 4) engage qualified expertise in urology in order to acquire samples of exfoliated cells from adequate populations of bladder cancer patients. The grantees would develop a cohesive plan for clinical studies which would take advantage of the research opportunities offered by existing bladder cancer patient populations.

Inter-disciplinary collaboration needs to be established in order to develop cell markers as powerful prognostic tools in patient management. Before an application of cell markers can become routine in clinical practice, there is a need to achieve close interaction among experts in cell markers, automated cytometry and urology. The collaborative approach projected in this RFA would make the best use of patient resources and would make it possible to correlate different kinds of markers, and to test and compare techniques and interpretations in different clinical settings.

BACKGROUND

The availability of exfoliated normal and neoplastic cell populations from the full endothelial surface of the bladder coupled with advances in cell markers and automated cytometry provides the bladder cancer field with a special opportunity for rapid progress. There is high potential that a collaborative research effort in this area would provide the marker-automated system needed for reducing costs in the area of bladder cancer diagnosis and prognosis. In the proper clinical setting, especially for patients with low-stage bladder tumors, automated cytometry of relevant cell markers might be practical as an outpatient urologic examination. Its increased use could reduce the need for cystoscopy.

ELIGIBILITY

It is the intent of this RFA to initiate studies among organizations which are already contributing significantly to research in cell markers. Applicant organizations are required to have the capacity for establishing liaison with investigators involved in clinical research in cancer, with a technical effort in automated cytometry, and with specific expertise in the intravesical treatment of bladder cancer patients or have the capacity to extablish liaison with such an organization. The principal investigator must have extensive experience in research in cell markers.

Organizations which currently have or can assemble these resources are encouraged to respond to this RFA. The awards should support only research done collaboratively among the network members. Core support for cell marker research, bladder cancer research and automated cytometry at the applicant organization and its affiliates should be funded through alternative sources. The required technical expertise, facilities, patient populations and qualified investigators should already exist in these organizations.

APPLICATION SUBMISSION AND REVIEW

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 8, 1987. It will not enter into the review of an application submitted in response to this RFA.

Applications responsive to this RFA will be reviewed for scientific merit by an appropriate peer review group composed primarily of non-Federal experts and set up by the Division of Extramural Activities, National Cancer Institute. Reviewers will consider each application in terms of its projected research plans, and of the proposed means for implementing collaborative network activities. Applications will be reviewed in competition with each other on a nationwide basis. This RFA solicitation is a single competition and has one specified deadline for receipt of applications.

MECHANISM OF SUPPORT

The mechanism of support for this program will be the NIH investigator-initiated research grant (R01). Awards may be made to non-profit and profit organizations. An applicant organization may apply for a period of support of up to three years. Funds, if awarded, would support research conducted by the collaborative network. The awards would also support travel, planning, communications and data management connected with the network effort.

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 three to five awards will be made at an annual total cost of approximately $560,000. Before the end of the three-year period of funding, the Bladder Cancer Network will be evaluated by the NCI and a means for possible continued or expanded support determined.

INQUIRIES

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

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

MOLECULAR APPROACHES TO PANCREATIC CANCER RESEARCH

RFA AVAILABLE: 87-CA-22

P.T. 34; K.W. 0715035, 0705025, 1002008, 0780000
National Cancer Institute

Application Receipt Date: July 15, 1987

The Division of Cancer Prevention and Control, through the Organ Systems Program, invites research grant applications from organizations which are capable of carrying out research in the molecular biology of pancreatic cancer.

OBJECTIVE AND SCOPE

The NCI proposes to encourage scientists in up to five existing molecular biology laboratories to develop a research capacity in the area of pancreatic cancer. Cooperation among these participating laboratories and sharing of resources would be encouraged. Investigators would have responsibility for planning and directing their own research programs, but collaborative arrangements among the laboratories would be forged as mutually beneficial circumstances arise. Participating laboratories would be responsible for identifying research objectives, developing research strategies, fostering collaborative arrangements, and developing means for resources development and allocation.

The major goal of this RFA is to increase understanding of the molecular mechanisms that regulate cytodifferentiation and morphogenesis in the transformed human exocrine pancreas. Cell(s) of origin for exocrine pancreatic cancer would be identified, and molecular tools would be developed for these tumor cells including specific probes for genes, oncogenes and gene products. Molecular probes would be developed for defining growth and differentiation of exocrine pancreatic tumor cells. Appropriate probes would be applied in the diagnosis and classification of human pancreatic tumors, and findings would be correlated with the clinical course of the disease. Transfected or infected cell lines would be selectively produced, expressing human genes and gene products related to growth, differentiation and transformation of exocrine pancreatic tumors.

BACKGROUND

Pancreatic cancer presents a challenging problem for basic and clinical scientists. Considerable progress has been made in defining the cellular, molecular and genetic origin of neoplasia in a number of malignancies, but similar research in pancreatic cancer has lagged considerably. This gap in information is due in part to the short time available for study of the disease between the time of diagnosis and death. About 25,000 new cases arise annually in the United States, 90% survive less than two years after diagnosis, and more than 98% die within five years. Current treatment regimens have been ineffective in significantly altering the survival of pancreatic cancer patients. Information on life-style factors which predispose towards this disease is scant and equivocal. It is obvious that a method for earlier diagnosis and a better understanding of the nature of pancreatic carcinogenesis are needed.

The active synthetic and secretory functions of the pancreas led to its use as one of the organs first studied at the cellular and molecular level. Considerable information is accumulating on the regulation and expression of genes related to the pancreatic secretory process, but little information is available concerning the onset, control and expression of the gene programs that drive normal cell differentiation in this gland.

ELIGIBILITY

It is the intent of this RFA to initiate studies of the pancreas in organizations which already are contributing significantly to research in molecular biology. An organization with a molecular biology laboratory, which can establish an association with a research effort in cancer, is encouraged to respond to this RFA. At the time of submission, core support for molecular biology and research in cancer, qualified investigators, technical expertise, facilities and patient populations should exist in the organizations which respond to this RFA. The principal investigator must have extensive experience in research in molecular biology.

Applicant organizations are required to have the capacity for establishing liaison with investigators involved in research in pancreatic cancer. The applicant organization should be involved in treating pancreatic cancer patients or have the capacity to establish liaison with such an organization. Applicants must propose research to be done primarily with pancreatic cancer cells. Work using normal cells from the pancreas or from other organs should be done for control purposes only.

APPLICATION SUBMISSION AND REVIEW

Each applicant will be responsible for developing details for research to be conducted within the applicant organization. Studies should also be described which might be facilitated through a collaborative sharing of expertise, facilities and resources among the participating laboratories.

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 8, 1987. It will not enter into the review of an application submitted in response to this RFA.

Applications responsive to this RFA will be reviewed for scientific merit by an appropriate peer review group composed primarily of non-Federal experts and set up by the Division of Extramural Activities, National Cancer Institute. Reviewers will consider each application in terms of its projected research plans, and of the proposed means for implementing collaborative activities. Applications will be reviewed in competition with each other on a nationwide basis. This RFA solicitation is a single competition and has one specific deadline for receipt of applications.

MECHANISM OF SUPPORT

The support mechanism for this program will be the NIH investigator-initiated research grant (R01). Awards will be made to non-profit and profit organizations. An applicant organization may apply for a period of support of up to three years. Funds, if awarded, would support research done within the applicant organization and research done collaboratively among the participating organizations. The awards would also support travel, planning, communications and data management connected with a collaborative effort.

Contingent upon the 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 annual total cost of approximately $600,000. Before the end of the three-year period of funding, the participating laboratories will be evaluated by the NCI and a means for possible continued or expanded support determined.

INQUIRIES

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
Bethesda, Maryland 20892-4200
Telephone:(301) 427-8818

BIOLOGICAL ROLE OF EXOCYCLIC NUCLEIC ACID DERIVATIVES IN CARCINOGENESIS

P.T. 34; K.W. 0715035, 0790010, 1007009

National Cancer Institute

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

The Division of Cancer Etiology (DCE) of the National Cancer Institute (NCI) invites grant applications from interested investigators for basic studies that are focused on providing insights and approaches to an understanding of the biological role of exocyclic nucleic acid derivatives in carcinogenesis. This is a reissuance of an announcement which first appeared in the NIH Guide for Grants and Contracts in Vol. 15, No. 2, January 31, 1986.

BACKGROUND

The current status of research on the types of adducts produced by exposure to vinyl halides, alkyl carbamates, mono and bifunctional aldehydes, epoxides, halonitrosoureas and related compounds and their role in carcinogenesis and mutagenesis was discussed at a workshop entitled "Cyclic Nucleic Acid Adducts in Carcinogenesis" which was held at the International Agency for Research on Cancer in Lyon, France on September 17-19, 1984. A report of this meeting has been published (see Cancer Research 45: 5205-5209, 1985). A number of chemicals of the above types which include known or suspected human carcinogens (vinyl chloride, acrylonitrile, cyclophosphamide), several of which can be found in food and beverages (ethyl, carbamate, methylglyoxal, glycidaldehyde, malonaldehyde, N-nitrosopyrrolidine), chemotherapeutic agents (haloethylnitrosoureas) and others which humans are exposed to as environmental pollutants (acrolein, also detected in cigarette smoke) or through occupational exposure (acrylonitrile, vinyl chloride) have been shown to form a large variety of adducts with guanosine, adenosine, and cytosine in nucleic acids. In addition, many of the compounds can also form interstrand crosslinks. From discussions on the mutagenicity and carcinogenicity of compounds such as vinyl chloride, acrylonitrile, methylglyoxal, ethyl carbamate and malonaldehyde, it was concluded that cyclic nucleic acid adducts could play a major role in the biological activity of these compounds. However, more work is needed since adducts of this type have not been identified in vivo for many compounds. The identification of adducts in DNA was determined to be a problem due to the lack of sensitive methods for the quantitation and identification of the adducts formed. It was also apparent that little is known about the repair of known exocyclic derivatives in mammalian cells.

This program is described in the Catalog of Federal Domestic Assistance number 13.393, Cancer Cause and Prevention Research. Awards are under authorization of the Public Health Service Act, Section 301(c) and Section 402 (Public Law-78-410, as amended; 42 USC 241; 42 USC 282) and administered under PHS grant policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or to Health Systems Agency Review.

OBJECTIVES AND SCOPE

It is the intent of this program announcement to encourage basic mechanistic studies focused on determining the formation, repair and relevance to muta genesis and carcinogenesis of exocyclic nucleic acid derivatives. It is not intended to make or imply any delimitation to the research supported by the Chemical and Physical Carcinogenesis Program of the Division of Cancer Etiology. The compounds of interest which are known or are likely to form exocyclic nucleic acid derivatives include: vinyl halides (vinyl chloride, vinyl bromide), alkyl carbamates (ethyl and vinyl carbamate), halonitrosoureas (BCNU, CCNU), monofunctional unsaturated aldehydes (acrolein, crotonaldehyde), bifunctional aldehyes (glyoxal, malonaldehyde, glycidaldehyde), beta-propiolactone, acrylonitrile, N-nitrosopyrrolidine and related cyclic nitrosamines, and some halogenated ethers and aldehydes (chloro- and bromoacetaldehyde). Examples of important areas of research emphasis include the following: 1) the identification and quantitation of adducts which may be responsible for the carcinogenicity of the test compound in animals, the transformation of cells in culture, or the mutagenicity of the compound in cells in culture or in other test systems; 2) the formation and repair of exocyclic adducts in animals, cells in culture, or test organisms relevant to carcinogenicity, transformation of mutagenicity studies; and 3) the mechanism of mutagenesis or carcinogenesis by exocyclic nucleic acid adducts, other adducts of biological interest or crosslinks which may be formed by the above mentioned compounds. It is also recognized that there will be a need to develop more sensitive methods to analyze and quantitate the many possible adducts and to detect them in DNA from

cells exposed to the chosen compounds. A desired sensitive method, not widely available, is an immunoassay using monoclonal antibodies to the chosen exocyclic adduct or other relevant adduct.

METHOD OF APPLYING

Any non-profit and for-profit institution, domestic and foreign, may apply. All PHS and NIH grants policies governing regular research project grants, including cost sharing, will apply to applications received in response to this announcement. Applications should be submitted on form PHS 398, Grant Application Kit, which is available in the grants and contracts business office at most academic and research institutions. Copies may also be requested by writing to:

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

Please type "Exocyclic Nucleic Acid Derivatives in Carcinogenesis" in item 2 on the face page of the application.

The original and six copies of the application should be sent or delivered to:

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

DEADLINE

Applications will be accepted in accordance with the usual National Institutes of Health (NIH) receipt dates for new applications. Deadline dates are: June 1, October 1, February 1. Earliest possible start dates would be: April 1, July 1, December 1, respectively.

REVIEW PROCEDURES AND CRITERIA

Applications in response to this announcement will be reviewed in accordance with the usual NIH peer review procedures. They will first be reviewed for scientific and technical merit by an appropriate review group composed mostly of non-Federal scientific consultants. Following this initial review, the application will be secondarily evaluated by an appropriate National Advisory Board or Council. The review criteria customarily employed by the NIH for regular research grant applications will prevail.

STAFF CONTACT

For further information, investigators are encouraged to contact:

Dr. Paul Okano
Chemical and Physical Carcinogenesis Branch
Division of Cancer Etiology
National Cancer Institute
Landow Building - Room 9C18
7910 Woodmont Avenue
Bethesda, Maryland 20892
Telephone: (301) 496-4141

In order to alert the Division of Cancer Etiology to the submission of proposals with primary thrust directed to chemical and physical carcinogenesis research, applicants are encouraged to contact Dr. Okano.

THE ROLE OF OMEGA-3 POLYUNSATURATED FATTY ACIDS IN CANCER PREVENTION

P.T. 34; K.W. 0715035, 0745055, 0710095

National Cancer Institute

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

The Division of Cancer Etiology (DCE) of the National Cancer Institute (NCI) invites grant applications from interested investigators for basic studies that are focused on providing insights and approaches to an understanding of the role of omega-3 polyunsaturated fatty acids in cancer prevention. This is a reissuance of an announcement which first appeared in the NIH Guide for Grants and Contracts in Vol. 15, No. 15, August 22, 1986.

BACKGROUND INFORMATION

It has been generally observed that the risk of developing cancer at certain sites (e.g. breast, colon, prostate, pancreas, endometrium and ovary) is higher among people who consume diets high in fat and low in vegetables, fruits, whole grains and other fiber-rich foods. Additionally, recent studies have suggested that not only the amount of fat, but the composition and type of fat consumed may have a significant influence on the development of cancer.

Fats containing polyunsaturated fatty acids (PUFA) of the omega-6 family are apparently more favorable to the growth of tumor cells. The PUFA generally con sumed are derived from vegetable oils which contain high levels of linoleic acid. Experiments with laboratory animals have demonstrated that dietary lin oleic acid favors the growth of tumor cells. The mechanism(s) of fatty acid enhanced tumorigenesis and tumor growth are not well defined. Possible mechan isms include the fact that polyunsaturated fatty acids can easily undergo oxida tion to yield a variety of potential mutagens, promoters, and carcinogens, such as fatty acid hydroperoxides, endoperoxides, enals, aldehydes, alkoxy, and hydro peroxy radicals which promote the growth of cancer cells. In addition, polyun saturated fatty acids like linoleic acid give rise to arachidonic acid when elongated and desaturated. Arachidonic acid is the precursor for biologically active prostaglandins, such as prostaglandin E2 (PGE2). PGE2 exerts suppressive action on immunological cells, which is postulated to enable tumor cells to escape the immunosurveillance of the body and metastasize and proliferate. There is evidence that omega-6 PUFA are conducive to promotion of cancer by virtue of their ability to elicit production of immunosuppressive prostaglandins.

This program is described in the Catalog of Federal Domestic Assistance number 13.393, Cancer Cause and Prevention Research. Awards are under authorization of the Public Health Service Act, Section 301(c) and Section 402 (Public Law-78-410, as amended; 42 USC 241; 42 USC 282) and administered under PHS grant policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to Health Systems Agency Review or to the intergovernmental review requirements of Executive Order 12372.

It is not feasible to eliminate PUFA completely from the human diet to reduce the risk of cancer because these PUFA are needed for normal biochemical functions and the maintenance of normal health. Furthermore, there is widespread advocacy for increased consumption of omega-6 PUFA (vegetable oils) to lower serum cholesterol levels (especially HDL cholesterol) and reduce coronary heart disease.

Ideally, we need a source of dietary PUFA that would exert beneficial effects on overt coronary heart and neoplastic disease while also suppressing the develop ment of these afflictions. The omega-3 PUFA which occur in fish oils, particu larly from fish that live in deep, cold waters, may serve that function. Fish oils extracted from mackerel, bluefish, herring, and menhaden, for instance, have low levels of omega-6 fatty acids, but contain high levels of omega-3 PUFA, such as eicosapentaenoic acid (20:5) and docosahexaenoic acid (22:6). Epidemiological studies with Greenland Eskimos, Japanese, and Icelanders indicate that popula tions consuming seafood regularly are less prone to coronary heart diseases, atherosclerosis, hypertension, and some types of cancer, such as those in the mammary gland and colon. However, changes in their food habits to western style diets is correlated with increased mortality rates from such cancers. Recent studies have demonstrated that diets containing these omega-3 fatty acids effectively retard the growth of tumor cells in animal models. Despite these various observations, the mechanisms underlying the relationship between dietary fat and cancer are not well understood.

A few examples can be cited in which experimental observations are related to possible mechanistic hypotheses of fish oil efficacy in the therapy and pre vention of cancer. Thus, it has been generally observed that the high serum levels of PGE2 derived from omega-6 PUFA are conducive to the growth of tumor cells and there is a good correlation between the levels of prostaglandin E2 and tumor growth in experimental animals. Fish oil enriched diets decrease the formation of PGE2, and this coincides with the retarded growth of tumor cells. In this respect, monocyte-macrophages are important relevant cells which are the major producers of PGE2. Massive invasions of macrophages have been observed in tumors. Because of the presence of high levels of PGE2 these macrophages do not function in their normal capacity as cytotoxic cells against tumors. However, by reducing the local concentrations of PGE2, the suppressive action of PGE2 on macrophage function could be relieved. Dietary intervention with fish oils may provide such an approach. It has been demonstrated that macrophages can effec tively take up omega-3 fatty acids from dietary sources. This reduces cellular arachidonic acid levels, and subsequently decreases their capacity to synthesize PGE2. Thus, the overall levels of PGE2 can be decreased by dietary omega-3 fatty acids, and thereby relieve the inhibition of the phagocytic activity of the macrophages. This could retard the growth of tumor cells. In addition, it has been observed that omega-3 fatty acid enrichment also enhances arginase pro duction in macrophages, and this enzyme exerts

cytolytic action on tumors. Thus, dietary omega-3 fatty acids could significantly retard the growth of tumor cells without affecting the normal functions of macrophages. Significantly, the omega-3 PUFA of fish oils may, by inhibiting cyclooxygenase and reducing PGE2 synthesis, divert the arachidonic acid into the lipoxygenase pathway which produces compounds such as hydroxyeicosatetraenoic acid (HETE) and leukotrienes (LT), e.g., LTB4. These compounds are chemotactic agents for macrophages and other immunological cells, which function in the control of tumors. Most significantly, HETE inhibits the growth of tumor cells.

Of especial interest have been recent studies directed at determining the potential effectiveness of dietary fish oils in cancer prevention in animals. Although results are only preliminary at this time, high levels of dietary fish oil (menhaden oil) appear to inhibit or retard the development of MNU-induced mammary tumors, and the development of azaserine-induced putative preneoplastic lesions of the rat pancreas. In addition, fish oils contain high levels of retinoids (Vitamin A) which can act as antineoplastic agents. Furthermore, another recent study indicates that a diet high in menhaden fish oil does not promote chemically-induced colon carcinogenesis, in contrast to a parallel-fed diet high in corn oil-derived omega-6 PUFA. Hence, omega-3 PUFA may act via a number of mechanisms. These observations suggest that fish oils and/or seafood-based diets may provide an effective non-invasive dietary intervention approach for reducing the risk of tumor growth and cancer.

RESEARCH OBJECTIVES AND SCOPE

The Chemical and Physical Carcinogenesis Branch is issuing this Program Announcement to encourage basic mechanistic studies on the role of omega-3 polyunsaturated fatty acids in cancer prevention. Among the areas of particular interest are: (1) anticarcinogenesis studies in various organ systems, particularly those organ systems in which the type and level of fat have been shown to play a role; (2) determination of whether efficacy obtains during the initiation period by modifying the susceptibility of the host to early events, or whether these fatty acids modulate the carcinogenic response in the post-initiation period, or both, and including determination of efficacy over the lifetime of the animal; (3) pharmacokinetic studies on the absorption, distribution, metabolism and excretion of these fatty acids, including such studies performed under the experimental conditions demonstrating cancer prevention; (4) studies on toxicology of the agents, including life-time administration studies under defined dietary conditions in several species of animals; (5) comparative metabolic studies in human vs animal systems; (6) indepth studies of mechanisms of action, especially as related to conditions known or demonstrating anticarcinogenic efficacy. It is particularly desired that mechanism studies on anticarcinogenesis be reflective of the current state-of-the-art in molecular and cellular carcinogenesis, experimental pathology, immunology, endocrinology, cocarcinogenesis and tumor promotion. Program Projects or consortial arrangements under traditional R01 grants where collaborating expertise, special facilities and equipment are deemed necessary to approach and carry out these investigations are encouraged.

METHOD OF APPLYING

Any non-profit and for-profit institution, domestic and foreign, may apply. All PHS and NIH grants policies governing regular research project grants will apply to applications received in response to this announcement. Applications should be submitted on form PHS 398, Grant Application Kit, which is available in the grants and contracts business office at most academic and research institutions. Copies may also be requested by writing to:

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

Please type "The Role of Omega-3 PUFA in Cancer Prevention" in item 2 on the face page of the application.

The original and six copies of the application should be sent or delivered to:

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

DEADLINE

Applications will be accepted in accordance with the usual National Institutes of Health (NIH) receipt dates for new applications. Deadline dates are: June 1, October 1, and February 1. Earliest possible start dates would be: April 1, July 1, and December 1, respectively.

REVIEW PROCEDURES AND CRITERIA

Applications in response to this announcement will be reviewed in accor dance with the usual NIH peer review procedures. They will first be re viewed for scientific and technical merit by an appropriate review group composed mostly of non-Federal scientific consultants. Following this initial review, the application will be secondarily evaluated by an appro priate National Advisory Board or Council. The review criteria customarily employed by the NIH for regular research grant applications will prevail.

STAFF CONTACT

For further information, investigators are encouraged to contact:

Dr. Carl E. Smith
Chemical and Physical
Carcinogenesis Branch
Division of Cancer Etiology
National Cancer Institute
Landow Building - Room 9B-06
7910 Woodmont Avenue
Bethesda, Maryland 20892
Telephone: (301) 496-4141

Dr. David G. Longfellow
Chief, Chemical and Physical
Carcinogenesis Branch
Division of Cancer Etiology
National Cancer Institute
Landow Building - Room 9A-02
7910 Woodmont Avenue
Bethesda, Maryland 20892
Telephone: (301) 496-5471

In order to alert the Division of Cancer Etiology to the submission of proposals with primary thrust directed to chemical and physical carcinogenesis research, applicants are encouraged to contact Dr. Smith.

RESEARCH ON MUSCULOSKELETAL FITNESS AND SPORTS MEDICINE

P.T. 34; K.W. 0705050, 0785205

National Institute of Arthritis and Musculoskeletal and Skin Diseases

PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) invites investigator-initiated research grant applications to study a broad range of basic and clinical topics related to musculoskeletal fitness and sports medicine. Support will be through individual research and career development grants.

BACKGROUND

Sports activities and fitness programs are very popular. More than 30 million young Americans participate in organized competitive sports, and one of every two adult Americans exercises regularly. This emphasis on activity has led to an improvement in physical fitness and an increase in activity-related injuries. Past research efforts have yielded many improvements in training athletes, preventing injuries and treating patients. However, further significant advances could be made with additional research to study basic and applied aspects of musculoskeletal exercise, training and sports-related injuries.

The magnitude of the sports injury problem is substantial, extending beyond sports into its impact on the workforce. It has been estimated that 17 million persons in this country sustain significant injury from sports or recreational participation yearly. Each year there are one million football injuries among high school participants and 200,000 ski injuries requiring treatment. One-third of the 15 million joggers will sustain an injury which involves the musculoskeletal system. It is clear that understanding the causes, prevention, and treatment of athletic and recreational injury is a major health issue.

Many of the advances in sports medicine have been of a technological nature. For example, a substantial improvement in the evaluation and treatment of sports-related joint injuries has been the development of arthroscopes. This device allows rapid visualization and repair of the interior of many injured joints.

There has not been a strong scientific research basis to support many of the currently recommended practices in this field. For example, while a strong scientific understanding of the normal physiology of muscle exists, there is not a large base of research into muscle metabolism, hypertrophy and injury during exercise, disuse, and strength training. Another example is the empirical design of many protective devices that are not founded in fundamental biomechanical studies.

Improved knowledge can be gained through increased basic science research related to sports medicine as well as in applying the information gained to practical problems in this field.

OBJECTIVES

This solicitation is intended to stimulate research that provides a new and expanded foundation of basic science knowledge related to musculoskeletal fitness and sports medicine. Additionally, it is intended to encourage applications of the best available scientific information in important clinical aspects related to training, prevention, treatment and rehabilitation.

SCOPE

A wide range of basic and applied research is desired in various aspects of musculoskeletal fitness. No order or priority of areas of interest has been established. Applicants are encouraged to submit high scientific quality research projects in any area related to the broad objectives of this announcement.

Examples of investigations of interest to the NIAMS include but are not limited to research on:

1 Muscle Pathophysiology - Studies on the metabolic, structural and protein changes occurring in muscles (and muscle-tendon junctions) during exercise, disuse, and strength training. Investigations of the damage and healing of muscle tissue from factors such as mechanical or thermal overloading or systemic biochemical changes. Develop a mechanistic understanding of the growth and maturation of muscle. Explore the interrelationships and molecular steps between mechanical stimuli and biochemical changes.

2 Epidemiology - Define the incidence and natural history of injury in competitive sports and recreational activities. Establish risk factors for incurring injuries and for the progression of an injury to a more serious medical problem. Determine if chronic and acute injuries are interrelated.

3 Clinical Studies - Provide improved repair and replacement of injured muscle, connective tissues and joints. Advancements in materials and methods for transplantation, augmentation, and replacement of ligaments and tendons. Common sports injuries and symptoms include ligaments of the knee (such as anterior cruciate ligaments and medial collateral ligaments), patellar pain, and rotator cuff syndrome. Enhanced understanding of non-surgical methods to treat injuries. Improved knowledge of the theory and practice of rehabilitation as it relates to sports injuries.

4 Functional Assessment - Establish simple, quantitative measures of joint motion and forces that may be uniformly applied at most research and clinical sites. Document the utilization of such evaluations for improved pre-injury screening and post-injury surveillance.

5 Injury Mechanisms - Determine the mechanical forces and biochemical environments that weaken and injure connective tissues. Establish the forces and force distributions within joint structures and tissues, both during normal function and during trauma. Establish the conditions present during competitive sports and recreational activities that may lead to damaged tissue. Compare overuse versus traumatic injuries. Investigate the role of neuromuscular control in injuries.

6 Healing - Improved general understanding of the natural healing process for muscle and connective tissue. Determine what interventions are most successful in enhancing healing and under what conditions should these therapies be applied. Establish the role of inflammation in healing and subsequent injury. Investigate healing from micro tissue damage as a preliminary step in strengthening and/or enlarging muscle and other connective tissue.

7 Prevention and Training - Develop improved protective sporting equipment and training methods, especially for high risk competitive and recreational activities. Determine the short and long range benefits and side-effects from using anabolic steroids. Establish more completely the interrelations between neuromuscular and connective tissue response to training.

General Considerations - A large research effort is required to establish a firm scientific foundation for a basic and applied program in musculoskeletal fitness and sports medicine. Improved knowledge is desired in several aspects of musculoskeletal fitness and injury: performing the activity, training and prevention, treatment, and rehabilitation. Research in these areas may be performed on various types of individuals, such as young children, adolescents, mature adults, aged, professional athletes, men or women. Because the appropriate fitness information may be different for each type of individual as they experience different possible phases of musculoskeletal fitness or injury, research should be carefully directed to the results applied to a particular combination.

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 grants (Study Section). 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 Initial Review Group and National Institute of Arthritis and Musculoskeletal and Skin Diseases Advisory Council recommendations. Applications should be submitted on form PHS-398, 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 new applications on an indefinite basis:

February 1, June 1, October 1

The phrase "RESPONSE TO NIAMS PROGRAM ANNOUNCEMENT: RESEARCH ON MUSCULOSKELETAL FITNESS AND SPORTS MEDICINE" should be typed on line 2 of the face page of the application. The original and six copies 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
Telephone: (301) 496-7326

Richard W. Lymn, Ph.D.
Muscle Biology Program Director
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Telephone: (301) 496-7495

This program is described in the Catalog of Federal Domestic Assistance No. 13.846, Arthritis, Musculoskeletal and Skin Diseases 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.

ERRATA

DETERMINATION OF THE THERAPEUTIC USEFULNESS OF PURIFIED CYTOKINES IN CANCER MODELS

P.T. 34; K.W. 0740015, 0755020, 0415000

DETERMINATION OF THE THERAPEUTIC USEFULNESS OF MATURATION DIFFERENTIATION AND ANTI-GROWTH FACTOR SUBSTANCES IN CANCER MODELS

P.T. 34; K.W. 0415000, 0740015, 0760020, 0755020, 0780015

National Cancer Institute

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

The receipt dates for the above referenced Program Announcements were inadvertently given as February 1, July 1 and October 1 in the NIH Guide, Vol. 15, No. 8, June 20, 1986. The correct application receipt dates are February 1, June 1 and October 1.

*U.S. G.P.O. 1987-181-289:40039