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NCI, ADVISORS CONCUR ON NEED FOR NEW MECHANISM TO INCLUDE CANCER CONTROL, MINORITY CENTER NEEDS

NCI staff and advisors have reached overall concurrence on approaches to take in fostering development of new mechanisms for increasing support of cancer control activities in general and for those aimed at the problems of cancer in minorities in particular. The new mechanisms are cancer control consortia, which would be organized to support cancer control activities within a region; and cancer control cooperative groups, which would be set up

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In Brief

MARK KOCHEVAR NAMED NEW ADMINISTRATIVE OFFICER OF DCE; THOMAS NECHELES DIES SUDDENLY AT 51

MARK KOCHEVAR, who is administrative officer for the Clinical Oncology Program in NCI's Div. of Cancer Treatment, will move up to A/O of the Div. of Cancer Etiology Oct. 1. He replaces Steve Ficca, now the NCI deputy executive officer.... **THOMAS NECHELES,** cliniciam in the Biological Resources Branch of NCI's Biological Response Modifiers Program, died suddenly last week from a heart attack. He was 51. He had been with the program since last January working with the extramural clinical trials supported by BRMP.... **DIV. OF CANCER** Treatment still has three major staff vacancies to fill: deputy to director Bruce Chabner, a Senior Executive Service position for which the appointment will require approval of HHS Secretary Margaret Heckler; associate director to head the Biological Response Modifiers Program, for which applications are still being received; and associate director for the Radiation Research Program, which appears may never be filled unless (a) government salaries take a big leap upward or (b) the field of radiotherapy becomes so oversaturated that incomes in private practice drop precipitously. Chabner had hoped that the challenge of running the program which supports all NIH extramural research on imaging as well as NCI's radiotherapy research would be attractive to at least a few of the world's top people in the field, but so far, no one of the experience and stature the job demands has come forward.... **FRED RUZICKA** has been appointed chief of the Diagnostic Imaging Research Branch of DCT's Radiation Research Program.... **ROBERT CARLSON,** associate director of the Northern California Cancer Program in charge of the consortium center's Community Outreach Program, has taken on the additional job of executive officer of the Northern California Oncology Group.... **VIRGINIA SUPPERS,** who has been on the staff of the Biological Response Modifiers Program at Frederick Cancer Research Facility, has been named clinical projects administrator at the Litton Institute of Applied Biotechnology in Rockville, Md.

NEW GUIDELINES BEING DEVELOPED FOR CANCER CONTROL, MINORITIES CENTERS

(Continued from page 1)
to tackle specific cancer control projects such as clinical trials of preventive agents, screening, etc.

A brief outline of guidelines for a cancer control consortium was presented by Lucius Sinks, chief of the Cancer Centers Branch of the Div. of Cancer Prevention & Control, at last week's meeting of the Cancer Centers Planning Committee. It was emphasized that the outline was intended only as a basis for discussion, and suggestions by the committee members resulted in agreement to completely rewrite and expand the document.

Sinks, Associate Director for the Centers & Community Oncology Program Jerome Yates and their staffs will develop a new document and submit it to committee members by mail. Their responses will be incorporated into a further revision, which possibly could be presented to the Div. of Cancer Prevention & Control Board of Scientific Counselors at its winter meeting. Concurrence of the National Cancer Advisory Board also probably will be sought.

The NCAB has already approved the concept of a special category of cancer centers for minority institutions, with guidelines for core grant support more flexible than those currently in force for cancer center core grants.

The Centers Planning Committee, as well as the President's Cancer Panel, have been pondering demands from cancer centers for some new type of funding to replace the old cancer control core grants which helped centers establish cancer control activities in their regions. Those funds were phased out with the switch in emphasis to cancer control research, which left many worthwhile activities without support and no money to develop new projects.

The decision to proceed with a new mechanism to provide core support for both cancer control consortia, which could include existing centers, and minority institution core grants, was proposed in the draft document presented by Sinks. Although it will be extensively revised and amplified, it does provide a broad view of the developing theme:

Eligibility

*Must be several institutions which might include local and state public health departments and other local and regional organizations.

*The consortium must have a capacity to impact on control activities in the local region or minority populations. The local region may be several states or large urban areas within one state or crossing state boundaries, but not limited to the referral pattern of a single institution.

*It must have an organizational structure and respective consortium members' support which gives stability to the director's office. Ideally, the director should have an appointment in a local university faculty.

Review Criteria

*Eligibility as defined above must be met.

*The ability to gather data on cancer incidence and mortality in the local area or minority populations must be evident.

*Appropriateness of plans for developing research activities that impact on the local population and/or minorities must be presented. These plans should include ways in which clinical research is enhanced in cancer patients, plans for prevention and improvement of management of patients.

*While peer reviewed and funded cancer control research projects conducted by the consortium must be a goal, it is not mandatory. However, it will be a requirement that the consortium has appropriate plans to develop such research in its immediate future.

Committee members agreed emphatically on a number of points:

—The guidelines should be very loosely drawn and extremely flexible.

—The present guidelines for cancer center core grants should not be changed.

—The budget for the new mechanisms should not be drawn from the existing cancer centers budget.

The question of participation by local and state health departments was an issue. Dwight Janerich of the New York State Health Dept. pointed out that while some states have strong health departments, others do not. The committee agreed it would be a mistake to require health department participation but that it should be encouraged.

Richard Steckel, UCLA, and other committee members argued that developmental funds should be provided for in the guidelines.

NCI has made no determination yet on the amount of money that will be available for the new mechanisms.

Last week's meeting may have been the last for the Centers Planning Committee, an ex officio group of non federal advisors who have been meeting since last November. Sinks said another meeting might be called if that is necessary to wrap up development of the guidelines.

The committee's discussions have focused on new directions for cancer centers in the context of cancer control research and national goals for the year 2000; intent of Congress with respect to the establishment of cancer centers; ways to enhance existing cancer research resources through the integration of regional networking with community

resources and research efforts; and intercenter study collaboration.

NCI told the committee that it would like to advance cancer centers' capability to serve their respectively diverse and varying regions and increase the impact that centers have on achieving national cancer control objectives for the year 2000. Those objectives are:

1. Facilitate the rapid and widespread transfer of effective cancer care technology and treatment into clinical practice.

2. Promote the acceptance of the transfer of effective cancer care technology and treatment by the target audiences—community care physicians.

3. Stimulate and enhance the understanding and interrelationships between the different organizational forms of cancer care delivery.

a. Establish that there is a basis for participation (i.e., mutual benefit for all participants and institutions).

b. Identify on what objectives numbers 2 and 3 can be done (e.g., pain input for certain kinds of cancers; different technologies; NMR; supportive care; nutritional support).

The committee developed some working recommendations:

*Goals should be set for number, type, location, collaborative efforts of centers and their role in the 1990-2000 goals.

*Assessment of regional needs should be encouraged.

*New mechanisms for support of centers in underserved areas and/or at minority institutions should be developed, including planning grants, guideline modifications, and aggressive programs aimed at minorities to decrease mortality.

*An integrated national effort in cancer control involving centers should be developed, but there should be no requirement that every center participate.

*Existing cancer center core grants are functioning well and require little modification. Any changes made should not harm basic science.

*Centers should become involved in training replacement scientists for those retiring within the next decade or so.

*Core grant developmental funds should be considered to stimulate basic-clinical interactions.

*Increased support should be available for renovations and construction.

*A mechanism should be developed to replace and purchase needed shared equipment.

*Staff investigator salary support should be fixed on a more timely basis.

*Basic science centers should interact with clinical and comprehensive centers or other equivalent groups.

The committee became especially concerned about the matter of training by cancer centers, and a subcommittee was established to develop a strategy. It considered these issues:

a. A significant proportion of the senior scientists at cancer centers will be of retirement age within the next decade or so. It is important that a national effort be devoted toward the training of oncologists skilled in laboratory science, a process that can take five to 10 years. The centers should become involved in the training of these replacement scientists.

b. Increased support should be provided for training both pre and postdoctoral students, as well as academic physicians in laboratory research. To attract the best young scientists and clinicians into such a program, it is critical that adequate stipend levels be provided.

The subcommittee arrived at the following conclusions and recommendations:

a. There are adequate mechanisms available for training; therefore, no additional types of awards are recommended. It was felt that senior individual postdoctoral fellowships and clinical investigator awards could be used effectively to retrain and re-energize existing faculty, in disciplines with a deficit of trained investigators such as the radiation sciences. Cancer center directors should be made aware of the available training mechanisms.

b. The number of trainees supported by NCI is about 20 per cent below the average for the total of NIH. The subcommittee was concerned that the level of cancer trainees may drop below a critical point, and believed that it should not be below the personnel needs projected by the National Academy of Sciences Committee on National Needs for Biomedical and Behavioral Research Personnel. To accomplish this will require approximately a 25 per cent increase in the current number of trainees.

c. These concerns should be relayed to Congress as a means of sustaining the national cancer effort.

The full committee approved the subcommittee's report and recommendations.

One of the major concerns of NCI in the consideration of the role of cancer centers has been the problems and potential of consortium centers. That was the primary focus of the meeting of the President's Cancer Panel with representatives of the Northern California Cancer Program (**The Cancer Letter**, Sept. 14). NCI staff members recently met with representatives of another consortium center, the Illinois Cancer Council. Suggestions regarding the consortium as a model to be considered for a cancer center program which could promote optimal cancer control research that came out of

that meeting included the following points, as presented by NCI:

1. Fundamental to the success of a consortium is the basic premise that the consortial group can accomplish more than the sum of its parts on certain projects and that what the consortial group organizes to do does not conflict with what the university based participants are doing or are best able to do. Outreach activities, patient accrual for selected tumor sites, information transfer, development of population based data sets, etc. are some examples of cancer control research coverage which may be facilitated through establishment of a consortium.

2. ICC requires active membership participation, a committed directorship, a steering committee limited in size, and a mutuality of trust and confidence that more can be done by coming together than by going it alone.

3. Separate cancer center guidelines, or provisions in the current guidelines should be created to accomodate the uniqueness of consortia.

4. Longitudinal support for start up and development by NCI is essential. It takes years to develop some linkages.

5. Review criteria must be adopted to accomodate the consortium model.

6. Strong ties to the state, county and local health authorities help greatly.

7. The consortium cannot be all inclusive or meet all needs of the region.

8. Leadership of the consortium must be secure; a consorium should be able to mobilize and operate quickly; it must not be rigid; and it is particularly well suited to programs in epidemiology, cancer control, and clinical trials.

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs, citing the RFP number, to the individual named, the Blair building room number shown, National Cancer Institute, NIH, Bethesda, MD. 20205. Proposals may be hand delivered to the Blair building, 8300 Colesville Rd., Silver Spring, Md., but the U.S. Postal Service will not deliver there. RFP announcements from other agencies will include the complete mailing address at the end of each.

RFP NCI-CN-55437-46
Title: Preclinical toxicology of chemopreventive agents
Deadline: Nov. 15

The Div. of Cancer Prevention & Control is interested in establishing master agreement contracts for preclinical toxicology of chemopreventive agents.

A primary function of the chemoprevention program is the identification and evaluation of agents for possible utilization in clinical trials in humans. Candidate agents, whether from natural sources or synthesized, have been evaluated for anticancer efficacy in various screening tests. However, before a decision can be made as to their suitability for the phase 1 clinical trials in humans, they must be evaluated for toxicity in animals.

The basic objectives of this project will be to evaluate the acute, subacute/subchronic and chronic toxicity of designated agents. These studies will be performed in animals (rodents and dogs) and will include conventional short term studies, lifetime studies in rodents and dogs, and multigeneration teratogenecity studies. The agents would be given primarily by the oral route.

The government contemplates awarding a series of master agreements for this work seeking to establish a pool of qualified sources who will compete for the individual master agreement orders (designated chemopreventive agents to be evaluated).

A summary of the tasks required in the project are as follows:

Task 1—Perform acute toxicity, pilot dose range finding, and 13 week subchronic toxicity in rats and dogs by the oral route. Include, where appropriate, complete gross necropsies, histopathological examinations, and clinical laboratory studies.

Task 2—Develop a protocol for a pharmacokinetic profile for each investigational agent. The protocol and profile may build upon published data and data provided by the manufacturer of the agent or NCI staff. Additional studies necessary to complete the pharmacokinetic profiles for the rat and the dog shall be performed by the contractor. Pharmacokinetic studies will provide parameters of absorption, blood concentration time profiles, distribution, and excretion. Data on tissue concentration of the test agent, determined as part of the toxicology testing shall contribute to the pharmacokinetic profile. Information on manor metabolites shall be included in order to provide as complete a picture as possible of the overall distribution and fate of the test agent. Appropriate modeling shall be applied to determine probable pattern of distribution and compartmentalization. The first studies performed shall be designed to provide absorption and half life information necessary to plan the 90 day rat and dog toxicology studies. Perform studies.

Task 3—Develop and perform teratogenecity studies on chemopreventive agents that have the prospect of being administered to women of childbearing potential. These will be the standard segment 1, 2, and 3 studies as described in the "Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use," available from the contract specialist upon request. For efficiency, the male rats from the three month oral study may be used to initiate the male related reproductive toxicity studies.

Task 4—Perform chronic one year oral toxicity in

rats and dogs. Clinical laboratory studies and gross and microscopic necropsy findings are to be included.

It is estimated that up to four master agreement orders per year will be issued pursuant to the awards of the master agreement contracts.

Suitable facilities and equipment appropriate to accomplish tasks should be available. Animal holding facilities for dogs must be provided with adequate environmental containment. Animal facilities must meet LTAALAS specifications. Facilities must have design and maintenance capability to meet chemical and biological control; must comply with NCI carcinogens and handling standards; must comply with federal and state occupational health and environmental laws and regulations. On site data handling (computer), chemical, and pathological facilities and equipment should be available. Contractors must comply with requirements set forth in the FDA Good Laboratory Practice Regulations.

Contract Specialist: Deborah Smith-Castle
RCB Blair Bldg Rm 2A07
301-427-8745

RFP NIH-ES-84-20
Title: Correction—National Toxicology Program quality assurance data auditing support resource.
Deadline: Extended to Oct. 31

This RFP announced previously is hereby revised as follows:

The National Institute of Environmental Health Sciences is soliciting proposals from offerors having the capability and facilities to provide audit support services for the National Toxicology Program. This project will involve services primarily for the auditing of data submitted to the NTP archives or to various NTP components. These audits will determine the quality of data and will validate the technical reports and other publications prepared by NTP. This effort will encompass the following 10 functions which will be carried out based on priorities established by NTP.

Function 1—preaudit preparation. Function 2—data audits. Function 3—validation of reports. Function 4—audit reports identifying problems. Function 5—summary audit report and interpretation of impact. Function 6—file of audit reports. Function 7—common data file for each testing laboratory. Function 8—tracking of audits. Function 9—TOMS data auditing procedures. Function 10—On site data auditing.

Offerors will be required to assemble audit team(s). A single audit team will consist of toxicologists, one person year; analytical chemists, one person year; veterinarian, pharmacologist, biologist or pathologist, two person years; history technician, one person year. It is anticipated that at the minimum the total level of effort for this project will be three audit teams or 22.5 person years for each of the three years. Each offeror may propose one, two or three audit teams, and one or more awards will be made to attain the total level of effort required. Each audit team will be expected to audit 25 chronic animal studies (two species/two sexes, three dose groups) each year, or the equivalent in a combination of prechronic, chronic and other types of studies differing in experimental design or methodology.

Offerors may propose a team capable of performing at the minimum 12 audits per year. It is anticipated that the level of effort for such a team will be approximately half of the level of effort shown above. By the time of the award of this solicitation, the NTP archives will be located within a 25 mile radius of NIEHS at Research Triangle Park, N.C. While offerors will not be required to establish a facility within a certain proximity of NIEHS, the majority of the auditing activities will be carried out at the archives. The report preparation will be done at the audit support contractor's facilities.

A potential for conflict of interest may exist with offerors or individuals who have had or currently have other NTP contracts. It is essential that personnel assigned to this contract are in no way associated with NTP contracts which have performed the testing or have been involved in evaluating the results of the testing from which the data were generated. If personnel are proposed for this contract who have been previously involved in NTP activities or have been employed as direct personnel, a consultant or subcontractor by any of the NTP testing laboratories or other NTP service contractors, the offerors must explicitly explain in their technical proposal how they will make sure there will be no conflict of interest or any appearance thereof. No one will be allowed to audit his own data or use data generated by his past activities or other NTP projects. It is anticipated that the potential for conflicts of interest will be greatly reduced through award of multiple contracts. Multiple awards will allow NTP the flexibility in the assignment of audits so as to avoid where possible apparent conflicts of interest.

NIEHS Contracts Management Office (OAM)
Attn: Mary Armstead
PO Box 12874
Research Triangle Park, N.C. 27709
919-541-7893

RFA 84-CA-19
Title: Studies on bovine leukemia
Application receipt date: Nov. 15

The Div. of Cancer Etiology of NCI invites applications for cooperative agreements to support investigator initiated research in bovine leukemia. Studies of interest include but are not limited to: (1) research to determine the nature of the target cells that undergo neoplastic transformation in vivo in cattle and sheep; (2) investigations to search for and develop a sensitive lymphoid cell transformation assay in vitro and delineation of the cellular and molecular events that lead directly to the cell transformation event; (3) research to determine the nature of the different protein products of the viral genome, including those involved in cell transformation; (4) research to determine the nature of the transforming DNA sequences in BLV tumors and lymphocytes; (5) investiga-

tions on the BLV genome through nucleotide sequence analyses and comparison to the genomes of other retroviruses, including HTLV; (6) investigations to delineate the nature of the plasma blocking factor and its mode of regulation of the expression of BLV; and (7) investigations to determine the role of cellular immunity in infection and expression of disease.

Applicants funded under this RFA will be supported through the cooperative agreement mechanism. These are assistance relationships involving substantial involvement of NCI staff during the performance of the project. The nature of NCI staff participation is included in the RFA. The recipients will have primary responsibility for the development and conduct of research. NCI involvement will be in regard to coordinating and synthesizing the research effort in regard to approaches, methodologies, and exchange of information. The total project period for applications submitted in response to this RFA should be three years. The intent is to fund approximately four to five projects with a total program cost for all cooperative agreements under this RFA approximately $500,000 for FY 1985 first year funds. This funding level is dependent on the receipt of a sufficient number of applications of high merit. Although this program is included in the financial plans of NCI, the awards pursuant to this RFA are contingent upon the availability of funds for this purpose. The issuance of this RFA does not represent a guarantee that any funds will be awarded. No funds are available for the purchase of large capital equipment.

Complete copies of the RFA and additional information may be obtained from Padman Sarma, DVM, PhD, Program Director, RNA Virus Studies 1, Div. of Cancer Etiology, Landow Bldg Rm 9A22, Bethesda, Md. 20205, phone 301-496-9734.

RFA 84-CA-27
Title: Studies on human T cell leukema/lymphoma virus types 1 & 2
Application receipt date: Nov. 15

The Div. of Cancer Etiology invites applications for cooperative agreements to support investigator initiated research on HTLV type 1 and 2. Studies of interest include but are not limited to: (1) investigation of the viral genome of various substrains of HTLV including studies of the LTR, env and pX regions; (2) identification and characterization of viral genome protein products as a clue to determining if they are transforming proteins and to understand the functional activity of the resultant products; (3) investigations of virus integration sites in various systems and/or hosts to determine if the transforming function acts in the cis or trans mode; (4) investigations directed to characterizing the clinically relevant biological activities of the virus, especially its immunosuppressive and/or immunoregulatory effects on the host; (5) determination of the exact mode of horizontal transmission of the virus, including investigations of possible insect transmission; (6) studies in virus-host interactions, including geographical localization, determination of host range, endemic areas other than the Caribbean and Japan (i.e., Africa and the Far East) and localization and overlap of different types of HTLV virus; (7) characterization of HTLV like viruses of nonhuman primates and determination if there is an evolutionary link to HTLV; and (8) investigation of the possible use of vaccines to prevent or suppress the horizontally transmitted HTLV associated diseases.

Applications funded under this RFA will be supported through the cooperative agreement mechanism. The total project period for applications submitted in response to this RFA should be three years. The intent is to fund approximately five to seven projects with a total program cost of about $750,000 of FY 1985 funds for the first year.

Copies of the complete RFA and additional information may be obtained from Padman Sarma (see above RFA for address and phone).

RFA 84-CA-17
Title: The physiochemical effects of dietary fiber in humans
Letter of intent receipt date: Oct. 16
Application receipt date: Dec. 11

The Div. of Cancer Prevention & Control invites applications for cooperative agreements to support research on the physical, chemical and biologic effects of dietary fibers and their possible protecting role in carcinogenesis. Studies of potential interest to NCI include, but are not limited to, the effects of fiber on (1) fecal mutagenic activity, (2) fecal content of bile acids, and (3) colon cell kinetics, morphology, and physiology. Investigators are encouraged to be creative and to explore novel physiochemical effects of various fiber fractions. While some of these studies can only be done in animal models, the intent is that results from these studies shall be directly related to human carcinogenesis.

Applicants funded under this RFA will be supported through the cooperative agreement mechanism.

Copies of the complete RFA and additional information may be obtained from Elaine Lanza PhD, Diet & Cancer Branch, Blair Bldg Rm 619, NCI, Bethesda, Md. 20205, phone 301-427-8753.

RFA 84-CA-18
Title: Selected cancer prevention clinical trials
Application receipt date: Dec. 10

The Div. of Cancer Prevention & Control invites applications for cooperative agreements to support risk reduction clinical trials which are directed toward examining the role of various preventive agents and/or diet in the prevention of cancer. Studies of populations at increased risk to colon, breast, bladder, and head and neck cancer are particularly appropriate at this time. Studies of occupational cohorts who have been exposed to known initiators and/or promoters are also encouraged. Situations where the dose reponse to the promoter can be estimated are particularly relevant. Another category of possible prophylactic trials involve studies of populations at risk to second malignancies. For example, a number of studies have reported

that Hodgkin's disease patients treated with alkylating agents have an increased risk of leukemia. Several trials involving skin and lung cancer risk reductions with carotenoids and retinoid compounds have been implemented and additional studies at these sites with the agents indicated are not encouraged at this time.

Copies of the complete RFA and additional information may be obtained from Mary Ann Sestili, PhD, Blair Bldg Rm 616, NCI, Bethesda, Md. 20205, phone 301-427-8643.

RFA 84-CA-24
Title: Use of oncogene related products for cancer therapy
Application receipt date: Dec. 14

The Div. of Cancer Treatment invites grant applications from interested investigators for basic and applied studies to evaluate the therapeutic efficacy of oncogene related products in animal tumor models.

Biological response modifiers refers to agents or approaches that alter the relationship between tumor and host by modifying the host's biological response to tumor cells, with a resultant therapeutic benefit. The application of these agents with a primary intent of therapy is the major focus of the Biological Response Modifiers Program.

The components of the BRM program include immunoaugmenting, immunomodulating and immunosuppressive agents, interferons and interferon inducers, lymphokines, cytokines, antigrowth factors, thymic factors, tumor antigens and modifiers of tumor antigens on cell membranes, antitumor antibodies, antitumor cells, maturation, differentiation and tumor growth factors.

This RFA addresses use of oncogene and oncogene related products for cancer therapy in animal models. A number of cellular genes collectively called "proto" oncogenes have been identified which are involved in the control of cellular proliferation and differentiation and have been shown to be direct mediators of cell transformation. Activation of these cellular genes as oncogenes appears to play an important role in both initiation and maintenance of oncogenesis. Several "proto" oncogenes have been identified in the human genome and a number of these have been found to be expressed in the activated form in various human tumors. In tissue culture, inhibition of oncogene activity appears to be associated, in several instances, with reversion of the transformed state. Where functional products of oncogenes have been described, they have been localized to the cell membrane, cytoskeletal elements, or the nucleus. These all represent areas where alterations might be expected to lead to the expression of a malignant phenotype, such as lack of contact inhibition and uncontrolled cell division. Expansion of knowledge of how biological response modifiers and oncogenes interact through investigator initiated research could provide useful information for the future understanding of how oncogenesis is initiated and maintained and how immunity may be enhanced towards specific oncogene induced malignancies.

This RFA is intended to stimulate research that will develop and utilize oncogene products or reagents made against these products for therapy in animal model systems. Development of oncogene or oncogene related products for therapeutic evaluation may involve use of tumor associated membrane antigens for monoclonal antibody production and development of vaccines, use of monoclonal antibodies directed against growth factors or growth factor receptors controlled by or encoded by oncogenes or analysis of factors that inhibit the action of oncogene products that control cell division. Other reasonable approaches directed toward cancer therapy employing oncogene or oncogene related products or related reagents with antitumor potential may be proposed. Studies may involve the isolation and characterization of these products for the purpose of evaluating their ability to modify or alter tumor initiation, growth and/or metastases as well as stimulating cytotoxicity in vivo or in vitro through activation of macrophages, cytotoxic T cells or natural killer cells. Additional proposals involving studies on how oncogene or oncogene related products may interfere with specific immune functions will also be considered. Therapeutic potential may be evaluated in the treatment of transplanted, induced or spontaneous animal tumors or human tumor xenografts in nude athymic mice or rats.

For further information and a copy of the RFA contact Dr. Cedric Long, Acting Chief, Biological Resources Branch, BRMP, Frederick Cancer Research Facility, Bldg 426 Rm 1, Frederick, Md. 21701, phone 301-695-1098.

RFA 84-CA-25
Title: Innovative approaches to development of cancer chemopreventive agents
Application receipt date: Dec. 15

The Div. of Cancer Etiology invites investigator initiated research grant applications for basic studies emphasizing innovative approaches to the inhibition and/or suppression of carcinogenesis. These studies are especially needed since strategies for cancer prevention involving reduction or elimination of human exposure to environmental carcinogens may not always be possible, and since significant portions of the human cancer burden may be due to endogenous carcinogens, cocarcinogens, and promoters. Inhibition of the development of cancer by administration of chemical, biochemical, and biological compounds, which directly and/or indirectly inhibit the cancer producing effects of neoplastic and promoting substances, is well known in animal systems and may offer an alternate approach to human cancer prevention. Especially important in these new approaches, regardless of preventive agents employed, will be deep inquiries into the mechanisms of anticarcinogenesis which take full cognizance of the developing forefronts of molecular biology and carcinogenesis, cellular biology, mechanisms of carcinogenesis and genetic aspects of carcinogenesis such as genetic susceptibility and resistance in experimental animal systems (including known, well defined systems of

"spontaneous" tumorigenesis).

Specifically, this RFA seeks high quality, innovative approaches with agents of the applicants' choosing, which will emphasize any of the following areas:

A. Thorough studies on mechanisms of action. Studies are needed from both in vitro and in vivo perspectives.

B. The pharmacokinetics of promising agents should be established for optimizing dose and delivery schedule in chemoprevention and for deriving basic understandings of the absorption, distribution, metabolism and excretion of these agents during the course of chemoprevention.

C. Structure activity relationships of promising compounds should be investigated.

D. Comparative studies on pathways of metabolism should be pursued in human vs. animal systems in view of possible differences in biohandling and response.

E. Compounds showing particular promise in short term assays require animal studies to investigate their efficacy as blocking and/or suppressing agents of the carcinogenic process. In these animal studies, dose and pharmacokinetics vs. response relationships should be derived for those compounds demonstrating anticarcinogenic effectiveness. Investigations should develop time/response relationships for efficacy as well.

F. Toxicologic investigations coupled with appropriate metabolic and pharmacokinetics studies should be pursued on these blocking and/or suppressive compounds.

This RFA will use the traditional NIH grant. Responsibility for the planning, direction, and execution of the proposed research will be solely that of the applicant. The total project period for applications submitted in response to this RFA should not exceed four years. The intent is to fund multiple projects, with total costs amounting to approximately $1 million for the first year.

Copies of the RFA may be obtained from Dr. Carl Smith, Program Director, Chemical & Physical Carcinogenesis Branch, DCE, NCI, Landow Bldg Rm 9B06, Bethesda, Md. 20205, phone 301-496-4141.

RFA 84-CA-26
Title: Mutagens in human foods
Application receipt date: Dec. 15

The Div. of Cancer Etiology invites grant applications from interested investigators for basic studies intended to provide insights and approaches to an understanding of the possible role of food mutagens in human cancer causation.

Concern over the presence of mutagens in human foods is part of a large and growing interest in the role of diet in human cancer causation and in the possible inhibition of cancer by dietary means. In this context, the relevance of dietary mutagens derives from their genotoxic effects which could lead to cancer induction. Concern over dietary mutagens gains further emphasis from the widespread occurence of mutagens in human foods. Apart from the well publicized association of mutagens with charcoal broiled steak, mutagen formation has been reported to occur upon the boiling of beef stock, the broiling of hamburgers at a relatively modest surface temperature, the frying of potatoes, and the toasting of bread. Mutagens have also been found to be present in many vegetables, in alcoholic beverages, spices, coffee, and tea. Various contaminants may also constitute a source of mutagens present in human foods. According to one estimate, the foods and beverages ingested by an individual in the course of a single day might contain 1-2 grams of mutagens.

Purpose is to accelerate the development of additional understanding relative to the possible role, fate, and cancer relevance of known dietary mutagens commonly present in human foods. Applications should be responsive to one or more of the items selected from any one or from a combination of the following categories:

A. In depth, basic studies on a small number of mutagens selected from among those which are known to occur naturally in human foods, those found in human feces, and those human dietary mutagens the formation of which is associated with the processing and preparation of food; compounds of particular interest include, but are not limited to, the following six classes: (1) heteroaromatic amines of the carboline and imidoquinoline types; (2) hydroxylated flavonoids; (3) carbonyl compounds such as acrolein, malonaldehyde and methylglyoxal; (4) fecapentaenes; (5) endogenous N-nitroso compounds; and (6) aromatic hydrocarbons.

B. Development of analytical procedures for the quantitation of the foregoing mutagens in foods and for the quantitation of them and their respective metabolic products present in blood, body fluids and tissues, and feces.

C. In vitro and in vivo studies relative to the absorption, metabolism, and possible carcinogenicity of selected compounds such as quercetin and the human fecapentaenes. However, full scale animal bioassays will not be supported through this RFA.

This RFA will use the traditional NIH research project grant and all policies and requirements which normally govern the grant programs of the PHS apply. The total project period for applications submitted in response to this RFA should not exceed four years. The intent is to fund multiple individual research project grants with total costs at approximately $750,000 for the first year.

Copies of the RFA may be obtained from Dr. David Longfellow, Acting Chief, Chemical & Physical Carcinogenesis Branch, DCE, NCI, Landow Bldg Rm 9A02, Bethesda, Md. 20205, phone 301-496-5471.

The Cancer Letter _Editor Jerry D. Boyd

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