THE CANCER LETTER

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IL-2 Trials Proliferate; Biotherapeutics Sees NCI Proposal As Vindication Of Its Policies

Clinical trials of interleukin-2, with and without lymphokine activated killer cells, had already been initiated or were in various stages of planning at a number of institutions around the U.S. before NCI took its proposal for making the process more widely available to FDA (**The**

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In Brief

NCI's George Khoury Dies; Panel To Meet June 22 In Pittsburgh; Rosemary Mackey To Leave MDA

GEORGE KHOURY, chief of the Laboratory of Molelcular Biology in NCI's Div. of Cancer Etiology, died April 25 at the NIH Clinical Center after a long fight with lymphoma. He was 43. Khoury joined NCI in 1971 and soon became widely respected for his work in genetics and virology. He was appointed chief of the laboratory in 1980, and only recently was elected to the National Academy of Sciences. A memorial service was scheduled for May 17 at NIH's Masur Auditorium, and a scholarship fund in Khoury's name is being established at Princeton. He is survived by his wife, daughter and son . . . . **PRESIDENT'S CANCER** Panel will meet June 22 at the Univ. of Pittsburgh School of Medicine, Scaife Hall Lecture Room 6, 8:30 a.m.-noon. Agenda will include presentations on colorectal cancer and drug resistance. . . . **ROSEMARY MACKEY**, director of planning at M.D. Anderson Hospital, will leave June 1 to become vice president for corporate development at St. Luke's Hospital in Houston. . . . **DEBORAH HENDERSON** is the new special assistant to NIAID Director Anthony Fauci. Formerly with the AIDS Epidemiology Research Coordination Program, she replaces **Marguerite Donoghue** who will be senior associate for legislative affairs of the AIDS Action Council. . . . **RANDALL HARRIS**, senior resident in clinical pathology at Duke Univ., has been appointed chief of the American Health Foundation's Div. of Epidemiology, AHF President Ernst Wynder announced. In addition to his MD, Harris has a PhD in genetics and statistics. . . . **CORRECTION:** Two of the concepts for SBIR projects reported as approved by the Div. of Cancer Etiology Board of Scientific Counselors (**Cancer Economics**, April 17) were in fact disapproved. They were titled "Development of a Biostatistical Expert System for Epidemiologic Studies" and "Development of an Epidemiology Tutorial for Physicians and Students in the Medical Sciences."

Biotherapeutics Welcomes NCI Into "Patients As Partners" Strategy

(Continued from page 1)

Letter, May 1). The move to place Il-2/LAK into a modified "Group C" category and make it available to 38 comprehensive and clinical cancer centers will further widen availability of that technology, provided FDA concurs with the recommendation of its Oncologic Drugs Advisory Committee. FDA approval is likely, considering the support the proposal has from Commissioner Frank Young.

"Group C" drugs are those with demonstrated efficacy against one or more forms of cancer but which have not yet been approved for marketing by FDA. They are available through FDA approved INDs (investigational new drug applications) for use in research protocols. Until the Group C mechanism was established, only those patients entered into formal protocols operated by NCI, an academic institution or the clinical cooperative groups had access to those drugs, except for a few who received it through their physicians under "compassionate INDs."

Group C (Groups A and B are phase 1 and 2 drugs), under an agreement hammered out by NCI and FDA which ended an escalating battle between the two agencies in the mid-1970s, permitted NCI to distribute those drugs at no charge to any qualified physician who agreed to submit regular reports on use of the drugs and toxicities observed. Some of the drugs were obtained free from pharmaceutical firms, others were paid for by NCI.

The proposal submitted by NCI on IL-2/LAK will still make interleukin-2 available free to participating centers, since it will be provided at no cost by the manufacturers. However, those who get it through Group C will have to generate their own funds to pay for data collection and other aspects of clinical research usually supported by NCI. The usual patient care costs also will have to be picked up by the institutions, patients, third party payers, etc.

The NCI proposal comes at a time when its executives, particularly Director Vincent DeVita and Div. of Cancer Treatment Director Bruce Chabner, have spoken out sharply against "commercialization" of new cancer treatments which require payment by patients on research protocols.

"I have a strong and personal disagreement with the sale of these unproven therapies as offered by companies such as that led by Dr. (Robert) Oldham of Biotherapeutics, which is offering this treatment," Chabner said at the last meeting of the DCT Board of Scientific Counselors. "Let's not confuse legitimate scientific enquiry, which is costly and uncertain, but necessary, with the inappropriate entry of experimental therapies into medical use. . . We have a new problem to cope with, and that is the possibility that new therapies will be taken up by companies devoted to making a profit. . . Commercialization is a real problem because once something becomes so public, and the public expects it to work, then there is a potential for people with commercial interests to exploit that."

Board member John Niederhuber said he was "concerned about the commercialization of this because I think that is where more harm can be done to the unsuspecting and very frightened patients. I think we are going to see it not only with this, but in other diseases, such as AIDS."

"We'll just have to be very straightforward with the public when we make announcements like this," Chabner said. "It is very important to make it clear that these are not proven therapies, that they have no place in the general practice of medicine, and that there should be no expectation that every patient has to have such therapy at some point. . . The thing that frightens me is that there are now people willing to sell things like this that are totally out of the realm of routine care of cancer patients. There are indications that commercial companies are trying to expand nationwide to do this."

Niederhuber asked about bringing regulatory pressure to bear on the problem. "It really is the problem of the medical community to police itself," Chabner answered. "And, of course, the FDA, which is responsible for experimental therapies. Also, I think it is the responsibility of the biotechnology companies which produce things such as Il-2 and other lymphokines, to see that they don't fall into the hands prematurely of commercial firms that are going to sell them. I think this is one of those things that they have got to take seriously. I don't think that they have considered that up to this point."

On that issue, the producers of interleukin-2 don't seem to be worried about the primary target of Chabner's wrath, Biothera-

peutics Inc., the Franklin, TN, firm which was established by Oldham and his colleagues for the express purpose of offering experimental therapy to patients for a fee designed to make the company profitable.

Cetus Corp., one of the manufacturers of recombinant interleukin-2, is providing it to Biotherapeutics at no cost. Biotherapeutics says it is not charging its patients for Il-2; patient fees pay for the laboratory services required to activate the LAK cells.

Biotherapeutics, in fact, greeted the NCI Group C proposal, with its acknowledgement that patients, their insurers, and others would have to pick up most of the costs, with undisguised enthusiasm.

"This proposed expansion acknowledges the needs of cancer patients to access promising new technologies and the appropriateness of patient participation in the funding of clinical research," Biotherapeutics said in a news release issued under the name of Edward Lanphier, vice president for corporate development. "This decision adopts the 'patients as partners' strategy implemented in 1984 by Biotherapeutics. . . This concept is one of the underlying principles of Biotherapeutics. The partnership of patient, physician and research laboratory working together in the private sector to increase the patients' access to new technologies in cancer treatment represents a powerful new method for developing cancer therapeutics. Biotherapeutics is the first to establish this partnership which offers a new mechanism for providing seriously ill individuals access to the most promising scientific developments and the funding of cancer research. Further, this move is consistent with FDA's recently revised provisions relating to the use and sale of investigational new drugs. The proposed procedures are designed to facilitate the availability of investigational new drugs to seriously ill patients and would authorize the sale of an investigational drug in clinical trials.

"With the recognition by NCI that the patient can be a partner in the funding of these investigational protocols, several factors should be addressed," the Biotherapeutics news release continued. "First, what are the costs of these investigational protocols? What are the true costs to society? Biotherapeutics has initiated over 100 patient funded contracts in the interleukin-2/LAK cell protocol. Historically, when services are taken from the public sector, costs are often reduced, efficiencies increased and quality improved. Secondly, what will be the timing of these programs? While NCI has indicated that it will develop these laboratories, Biotherapeutics is up and running, and putting in place multiple certified facilities. The company has put in place the trained scientists, fundamental technologies, laboratory processes, and patient service programs that permit physicians in local communities access to the technologies necessary to aggressively utilize biotherapies."

Biotherapeutics received a big boost in its credibility when the "New England Journal of Medicine" published a report on the company's experience with Il-2/LAK in the same issue with the latest report by NCI's Steven Rosenberg.

Even better, from Biotherapeutics' standpoint, the regimen developed by Oldham, Biotherapeutics Medical Director William West and their colleagues, administering Il-2 through continuous infusion, produced results comparable to those reported by Rosenberg but with considerably less toxicity (West was the chief author of the NEJM article).

Biotherapeutics President Louis Berneman told **The Cancer Letter** that the NEJM article "is a confirmation of previously reported findings by an independent group of investigators of the activity of IL-2/LAK in notoriously resistant tumors [such confirmation is what NCI hopes to get from the six institution study it has been supporting for the past year]. It suggests that constant infusion of Il-2/LAK provides equivalent clinical response with less toxicity and increased patient safety and comfort as compared to bolus administration of Il-2. It is the first report of a safer, more efficient system for cell activation developed by Biotherapeutics. It is indicative of the high quality research that can be done in the private sector as a partnership between investors and patients. It demonstrates the feasibility of a new system designed to increase treatment opportunities for cancer patients."

Berneman added that Biotherapeutics has "demonstrated that this technology can be conducted by high quality investigators in the private sector and be applied to patients much more broadly than the current NCI patient eligibility criteria." Also, "the

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RFAs Available

RFA 87-CA-23

Title: Markers of exfoliated bladder cancer cells correlated with tumor progression and recurrence
Application receipt date: July 15

The Div. of Cancer Prevention & 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.

A major goal of this RFA is to stimulate the development of an interorganizational cell marker network for bladder cancer. 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 of 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) test 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.

Interdisciplinary 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.

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.

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 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 NCI and a means for possible continued or expanded support determined.

For further information and complete copies of the RFA, contact William Straile, PhD, Cancer Centers Branch, DCPC, NCI, Blair Bldg Rm 727, Bethesda, MD 20892, phone 301/427-8818.

RFA 87-CA-22

Title: Molecular approaches to pancreatic cancer research
Application receipt date: July 15

The Div. of Cancer Prevention & 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.

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. Cells of origin for exocrine pancreatic cancer would be identified, and molelcular 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 pancratic 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.

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 U.S., 90 percent survive less than two years after diagnosis, and more than 98 percent 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 molelcular 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.

Contingent on the availability of funds and dependent on receipt of enough 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 NCI and a means for possible continued or expanded support determined.

For further information and complete copies of the RFA, contact William Straile, PhD, Cancer Centers Branch, DCPC, NCI, Blair Bldg Rm 727, Bethesda, MD 20892, phone 301/427-8818.

Program Announcements

Title: Biological role of exocyclic nucleic acid derivatives in carcinogenesis
Application receipt dates: June 1, Oct. 1, Feb. 1

The Div. of Cancer Etiology invites grant applications ffor basic studies focused on providing insights and approaches to an understanding of the biological role of exocyclic nucleic acid derivatives in carcinogenesis.

It is the intent of this announcement to encourage basic mechanistic studies focused on determining the formation, repair and relevance to mutagenesis and carcinogenesis of exocyclic nucleic acid derivatives. It is not intended to make or imply any delimitation to the research supported by the Chemical & Physical Carcinogenesis Program of DCE. 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 aldehydes (glyoxal, malonaldehyde, glycidaldehyde), beta propiolactone, acrylonitrile, N-nitrosopyrrolidine and related cyclic notrosamines, and some halogenated ethers and aldehydes (chloro and bromoacetaldehyde).

Examples of important areas of research emphasis include (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.

In addition to submitting grant applications on PHS form 398 to the NIH Div. of Research Grants, applicants are encouraged to contact, for further information and to alert DCE on potential proposals, Dr. Paul Okano, Chemical & Physical Carcinogenesis Branch, DCE, NCI, Landow Bldg Rm 9C18, Bethesda, MD 20892, phone 301/496-4141.

Title: Role of omega-3 polyunsaturated fatty acids in cancer prevention.
Application receipt dates: June 1, Oct. 1, Feb. 1

The Div. of Cancer Etiology invites grant applications for basic studies 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 made last year.

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 no 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 consumed are derived from vegetable oils which contain high levels of linoleic acid. Experiments with laboratory animals have demonstrated that dietary linoleic acid favors the growth of tumor cells. The mechanisms of fatty acid enhanced tumorigenesis and tumor growth are not well defined. Possible mechanisms include the fact that polyunsaturated fatty acids can easily undergo oxidation to yield a variety of potential mutagens, promoters and carcinogens such as fatty acid hydroperoxides, endoperoxides, enals, aldehydes, alkoxy, and hydroperoxy radicals which promote the growth of cancer cells. In addition, polyunsaturated fatty acids like linoleic acid give rise to arachidonic acid when elongated and desaturated arachidonic acid is the precursor for biologically activate 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.

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 and reduce coronary heart disease.

Ideally, a source of dietary PUFA is needed that would exert beneficial effects on overt coronary heart and neoplastic disease while also suppressing the development of these afflications. The omega-3 PUFA which occur in fish oils, particularly 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 and docosahexaenoic acid. Epidemiological studies with Greenland Eskimos, Japanese and Icelanders indicate that populations consuming seafood regularly are less prone to coronary heart disease, 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.

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 lifetime administration studies under defined dietary conditions in several species of animals; (5) comparative metabolic studies in human vs. animal systems; (6) in depth 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 RO1 grants where collaborating expertise, special facilities and equipment are deemed necessary to approach and carry out these investigations are encouraged.

In addition to submitting regular NIH applications to the Div. of Research Grants, applicants are encouraged to contact for further information either Dr. Carl Smith, Chemical & Physical Carcinogenesis Branch, DCE, NCI, Landow Bldg Rm 9B-06, Bethesda, MD, phone 301/496-4141; or Dr. David Longfellow, Chief, Chemical & Physical Carcinogenesis Branch, DCE, NCI, Landow Bldg Rm 9A-02, Bethesda, MD 20892, phone 301/496-5471.

Title: NCI Outstanding Investigator Grant
Application receipt date: June 15

NCI will continue to accept applications for the Outstanding Investigator Grant, the purpose of which is to provide long term support to experienced investigators with outstanding records of research productivity. The OIG is intended to encourage investigators to embark on projects of unusual potential in ancer research. Emphasis will be placed on evidence of recent substantive contributions (i.e., seminal ideas and innovative approaches to resistant problems) and the potential for continued work of high caliber.

Applications may be submitted only by domestic institutions on behalf of investigators who have recently demonstrated outstanding research productivity for at least five years. There are no age restrictions. Only United States citizens, nationals or permanent residents may be presented as candidates for this grant.

Applications will be accepted only by NCI when they are cancer related as defined by the Div. of Research Grants grant referral guidelines. Thus, investigators whose current research support is derived predominantly from sources other than NCI may not be eligible and are encouraged to discuss their research objectives with appropriate NCI officials before applying.

The institution sponsoring the OIG application is required to commit itself to providing 25 percent of the investigator's salary support.

Applications which do not meet all of the above eligibility criteria or which have not had approval from NCI as exceptions to the above criteria will be returned.

The receipt date of all OIG applications will be June 15 of each year. They will be processed for review at the earliest possible meeting of the National Cancer Advisory Board.

(Editor's note: Among the advantages of OIG awards are that they are for seven year periods, providing long term, stable support for investigators without subjecting them to the more frequent review required by RO1s and PO1s; they wrap up into one grant all of the grant support an investigator may be receiving from NCI; they are renewable in recompetition; they are reviewed by mail by appropriate experts).

For further information and copies of the full text of the program announcement, contact Mrs. Barbara Bynum, Director, Div. of Extramural Activities, NCI, Bldg 31 Rm 10A03, Bethesda, MD 20892, phone 301/496-5147.

RFPs Available

Requests for proposals 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 20892. 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-CM-87219-16

Title: Master agreements for the large scale isolation of anti-AIDS agents from natural sources
Deadline: Approximately July 15

Master agreements are competitively negotiated and awarded to more than one contractor. It is planned that such agreements will be awarded on or about April 15, 1988, for a five year period of performance, but will not be funded per se. After award, master agreement holders will be invited to bid competitively on appropriate master agreement orders (MAOs) as they are issued. Each MAO will be designed to accomplish a specific task as promptly as possible and will be awarded on a completion or term (level of effort) basis as determined by the contracting officer.

The Developmental Therapeutics Program of NCI's Div. of Cancer Treatment is interested in receiving proposals from, and establishing master agreements with, offerors with the capability to extract, isolate and purify anti-AIDS agents from plant and animal materials on a pilot plant scale. Successful offerors must provide a pilot plant facility capable of storing and processing up to 5,000 kg of bulk crude material and must have experience in process development of natural products isolations. The government will supply the plant and animal materials to be processed and details of isolation processes.

The successful offerors will supply all equipment, solvents, reagents, and other materials needed for the project. The anti-AIDS agents isolated must be of high purity, suitable for subsequent manufacture of clinical dosage forms, ald all work must be carried out under current good manufacturing practices standards. A requirement is that the contractor be registered as a manufacturer of bulk drugs with the Food & Drug Administration at the time a master agreement order is awarded.

Contract Specialist: Patricia Shifflett
RCB Blair Bldg Rm 216
301/427-8737

RFP NCI-CM-87216-16

Title: Synthesis of congeners and prodrugs of anti-AIDS compounds
Deadline: Approximately July 15

The Drug Synthesis & Chemistry Branch of the Developmental Therapeutics Program has a requirement for contractors with chemical synthesis and drug design expertise to synthesize a variety of compounds

for evaluation as potential anti-AIDS agents.

The assigned objectives of this project will be (a) to design and synthesize congeners and prodrugs of compounds with confirmed activity; (b) to design and synthesize prodrugs and other compounds that possess elements of both congener and prodrug; (c) to synthesize compounds related to products of natural origin and other related heterocycles; and (d) to synthesize antisense nucleic acids.

Each contractor should have available a fully operational facility, including all necessary equipment and instrumentation for all aspects of the contract. The nature of this project requires that the following restrictions be applied:

NCI signs legally binding agreements with certain suppliers (often pharmaceutical or chemical companies) which state that all information on compounds submitted by the supplier will be held confidential. The successful offeror will be expected to synthetically modify such commercially confidential (discreet) materials. Thus, pharmaceutical or chemical companies could obtain valuable data on new lead compounds. Therefore, in order to honor the confidentiality agreement with the supplier, NCI believes that the compounds cannot be sent to potential competitors of the supplier, and, thus, pharmaceutical and chemical companies must be excluded from the competition.

The contract period is to be three years, beginning approximately April 1, 1988, at a level of effort of approximately 6,650 hours per year per contract. Three cost reimbursement contracts are expected to be awarded.

Contract Specialist: Patricia Shifflett
RCB Blair Bldg Rm 216
301/427-8737

RFP NCI-CM-87234

Title: Development and implementation of mechanistically oriented anti-HIV drug prescreens

Deadline for statement of qualifications: May 29

NCI is planning to award multiple contracts for development and implementation of mechanistically oriented anti-HIV drug prescreens. These contracts will address various aspects of the viral life cycle which may be exploited as therapeutic targets.

Infection of susceptible human cells by human immunodeficiency virus (HIV), the etiologic agent of acquired immune deficiency syndrome, has been shown to involve a series of steps common to other retroviral infections, i.e., binding of viral particles to cellular receptors, internalization of the virus, transcription of viral RNA into DNA via the viral enzyme reverse transcriptase, integration of the viral DNA transcript into host chromosomal DNA, and subsequent transcription of viral DNA resulting in the synthesis and release of new infective virions. These steps offer multiple possibilities for the development of new agents useful for therapeutic purposes. To date, efforts have centered on development of drugs which inhibit the viral reverse transcriptase enzyme and/or which can be shown to directly inhibit viral cytopathic effects in vitro. Other biochemical/molecular systems besides reverse transcriptase have received relatively little attention and none has been the focus for a large scale screening program.

In order to accomplish an effort of this nature, an organization must have the capability to develop and evaluate drug screening assays which address biochemical/molecular targets relevant to identification of compounds with potential anti-HIV activity. Work should be directed towards development of screening assay methodology which can be implemented on a scale suitable for testing at least 10,000 unknown materials annually. Following the demonstrated feasibility of proposed assay methods, the organization must be capable of implementing a large scale mechanistically oriented prescreen capable of testing at least 10,000 unknown materials annually.

Firms, individuals, or organizations should indicate their interest in developing and implementing a mechanistically oriented prescreening by responding no later than May 29. Respondents should briefly describe proposed assay methods and broad capabilities in a nonproprietary fashion and indicate experience and expertise in these areas.

This announcement is to solicit expressions of interest and information for purposes of program planning. It does not constitute an RFP and is not to be construed as a commitment by the government. Responses will be used to establish a source list for solicitation. Submit written responses to the contracting officer.

Contracting Officer: Clyde Williams
RCB Blair Bldg Rm 224
301/427-8737

RFP NCI-CP-71113-56

Title: Record linkage studies utilizing resources in population based tumor registries (master agreements)

Deadline: Approximately July 1

NCI wishes to contract with population based cancer registries in the United States and in other countries in order to collaborate in the conduct of record linkage and subsequent analytic studies.

Respondents should have cancer incidence data for all patients diagnosed within a defined geographic locale during the last decade, 1976-85. The respondents must have experience in the collection of cancer data from a variety of medical sources and multiple institutions. Respondents must have experience in obtaining information on vital status of cancer patients years after initial diagnosis. Respondents must have the legal authority to collect medical data within the given geographic area or else be able to demonstrate the willingness of all medical facilities within that area (including hospitals, clinics, private pathology laboratories, private radiotherapy facilities, and nursing homes with diagnostic services) to participate in data collection and patient followup activities.

Respondents must have, or the ability to obtain, access to existing population based registries of exposed groups of individuals in the geographic areas covered by the cancer registry. Respondents must be willing to conduct collaborative research studies and analyses with the Epidemiology & Biostatistics Program and be willing to permit the pooling of data with other cancer registries for combined analyses.

Master agreements will be awarded to all respondents whose technical proposal is considered acceptable.

The initial master agreement award is nonmonetary and is exclusively for the purpose of establishing a pool of contractors who are qualified to perform services for epidemiologic studies of cancer utilizing the resources of population based cancer registries. Each master agreement holder will be eligible to compete for awards of master agreement orders to carry out specific record linkage and subsequent analytic studies. Master agreement holders receiving a MAO award will be selected from among those with a master agreement who choose to compete for the MAO RFP, based on technical merit and budgetary considerations for the specific tasks involved.

This is a recompetition of existing master agreements for record linkage studies. Master agreements will be awarded for a four year period.

Contracting Officer: Nancy Coleman
RCB Blair Bldg Rm 114
301/427-8888

USC Opts For Its Own Trial Using Low Dose Il-2 With Cyclophosphamide

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semiclosed bag system we have developed significantly reduces risk of possible contamination and is a more cost and time efficient system."

Biotherapeutics said it is working actively "on the next generation of LAK cell therapy" and "a myriad of new technologies." These include "tumor derived activated killer cells (TDAK) which provide clinicians with tumor specific AK cells. These activated lymphocytes are derived from the patient's own tumor and may be more active than cells from the blood." [Sounds like the tumor infilatrating lymphocyte (TIL) technology Rosenberg has been working on, which he thinks may be 100 times as potent as Il-2/LAK].

In another new program, Biotherapeutics said it is working on "antibody targeted activated killer cells which combine the targeted delivery of monocolonal antibodies having affinity for individual patient tumors with the cytotoxic and antiproliferative activities of lymphokine activated killer cells."

An institution which would qualify as one of the 38 which could participate in the Group C study, the Univ. of Southern California Comprehensive Cancer Center, has chosen not to. USC announced that it will conduct independent trials of interleukin-2 for melanoma and kidney cancer patients rather than participate in the NCI program.

"Essentially, we are using lower doses of Il-2 and a different method of administration to achieve the same results as NCI," Malcolm Mitchell, professor of medicine and microbiology and principal investigator for the study, said. "And we are achieving these results without the severe side effects usually associated with this treatment."

Mitchell has added cyclophosphamide to the regimen to inhibit the production of suppressor cells that interfere with the effectiveness of Il-2.

In the NCI trial, Il-2 is incubated with white blood cells from the patient, outside the body, to produce the LAK cells. In the USC study, LAK cell production takes place within the body after the patient is injected with a low dose of Il-2.

Mitchell has treated 24 advanced melanoma patients to date. All of them had a recurrence of their disease following surgery, and some had failed other therapies as well. Six have had at least a partial remission--a 50 percent regression of disease lasting at least four weeks. One of the six has experienced complete remission of subcutaneous and cutaneous metastases; and, in another, eight large lesions in the liver disappeared.

An additional seven patients on the USC study showed regression of their cancer that was between 25 and 50 percent.

Results of the NCI trial were comparable, Mitchell said. Twenty six patients in the NCI group of 106 had melanoma. There were complete remissions in two and partial remissions in four.

Mitchell's regimen begins with a low dose injection of cyclophosphamide. Three days later, the patient begins to receive daily injections of Il-2 for two weeks (excluding weekends). After a one week break, another cycle begins. Each patient completes three cycles, after which he or she is evaluated. If there is at least a 25 percent regression of disease, he goes through another three cycles of therapy.

Patients who experience complete remission are taken off therapy after the second series of three cycles. Those who continue to show a partial remission are put on a maintenance regimen--one cycle of cyclophosphamide and Il-2 every six weeks.

Side effects of this treatment, which have been moderate, have included fever, chills, fatigue and joint pain.

"Our regimen has proven to be very tolerable to the patients," Mitchell said. "Fatigue has been the most common problem. But the breaks between cycles allow patients to recover their energy. We haven't had any patients drop out of the trial because of the side effects."

The USC trial for melanoma is ongoing, and another trial using Il-2 administered in the same way for kidney cancer has been initiated. For information on the USC trials, call 213/224-6707 or 224-6704.

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