THE CANCER LETTER

Vol. 16 No. 24
June 15, 1990

Price $195 Per Year US, Canada.
$220 Per Year Elsewhere

P.O. Box 15189 Washington, D.C. 20003 Telephone 202-543-7665

DCT Board Approves Concepts For Acoustic Microscopy, Taxol Development, AIDS R&D

A cooperative agreement for development of in vivo acoustic microscopy, which had not been greeted with enthusiasm previously, and a five year, $5 million program of grants to support development of the

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In Brief

Eight Minority CCOP Awards Confirmed, Four More Coming; General Motors Winners Named

EIGHT MINORITY CCOP applicants, identified as probable awardees by **The Cancer Letter** (June 1), have been confirmed by NCI. There will be four more minority CCOPs funded in this round, but NCI declined to identify them until the award process has been completed. The payline will be somewhat higher than the 220 previously reported. Two of the additional successful applicants had scores under 220, two over. There will be no exceptions funded (over the payline). A total of $1.95 million will be made available for the program in FY 1990 funds. . . .**GENERAL MOTORS** Award winners announced this week: David Cox, Oxford who received the Kettering Prize; Webster Cavenee, director of the Ludwig Institute for Cancer Research in Montreal, and Raymond White, cochairman of human genetics at the Univ. of Utah, who shared the Mott Prize; and Mark Ptashne, professor of biochemistry and molecular biology at Harvard, who received the Sloan Prize. . . . **GEORGE PALADE**, dean of scientific affairs at the Univ. of California (San Diego) School of Medicine, received the Memorial Sloan-Kettering Medal for Outstanding contributions to Biomedical Research at MSK Cancer Center's annual academic convocation. Among other honors for his work in cell biology, Palade received the Nobel Prize in 1974. Other awardees at the MSK convocation were **Neal Flomenberg** and **Stephen Rubin**, Boyer Young Investigator Awards; **Alfred Knudson**, senior member of the Institute for Cancer Research at Fox Chase Cancer Center, Judd Award for major advances toward the control and cure of cancer; and **Saul Rosenberg**, professor of medicine and radiation oncology at Stanford Univ. School of Medicine, C. Chester Stock Award for significant contributions to advancement of knowledge in cancer. . . . **JEAN JENKINS** is the chief of the Cancer Nursing Service at the NIH Clinical Center. She joined the Cancer Nursing Service in 1975 and has held a variety of positions there and with NCI's Div. of Cancer Treatment. She has been acting chief of the service for the past year. . . . **REP. RICHARD DURBIN** (D-IL) will address the Assn. of American Cancer Institutes at its annual meeting June 22, in Rochester, MN.

DCT Board Approves Concepts For New Radiation, Taxol Research

(Continued from page 1)

hottest new anticancer drug, taxol, received concept approval from the Div. of Cancer Treatment Board of Scientific Counselors last week.

The board also gave concept approval to $22 million worth of new grant and contract supported AIDS related projects and recompetition of contracts for the development of anti-AIDS agents.

The board had tabled the acoustic microscopy RFA at its last meeting (**The Cancer Letter**, March 2), suggesting that the filed needed more basic research before committing to equipment development. Radiation Research Program Director John Antoine agreed to bring it back in June with revisions.

Antoine and some of his colleagues believe that acoustic microscopy may make possible in vivo tissue microscopic analysis. "It may be better than MRI or at least its equal in some sites, and it will cost a lot less than MRI," Antoine told **The Cancer Letter.**

Two changes were apparent in the concept presented last week from that previously proposed: the length of the project was reduced from five to three years, with the annual commitment remaining at $800,000; and it would channel that support to an Acoustic Microscopy Research and Development Working Group, with representatives from the scientific and commercial communities.

The specific focus will be the development of a special small (18 gauge) transducer modified for in vivo acoustic microscopy and integrated with the circuits necessary for signal excitement, reception, transmission, and processing. The achievement of this goal requires a multidisciplinary approach using the unified concept system necessary to test and evaluate performance of the integrated transducer system at each stage of its development, the concept statement said. The working group would provide the means to that approach.

The board approved the concept with no negative votes, although Susan Horwitz, Yung-chi Cheng, and John Mendelsohn abstained.

Further details of this concept were included in the March 2 issue's account of the previous presentation.

Taxol "has shown excellent confirmed activity against refractory ovarian cancer and preliminary activity at other sites," the concept statement for biological and chemical studies of the agent states. "It is one of the most promising new drugs in many years. It has a wholly novel mechanism of action, binding to microtubules and stabilizing them against depolymerization. Investigations of the chemistry, biology, biochemistry, and pharmacology of taxol have been limited, and many aspects of drug production in the source plants, taxus species, as well as many aspects of drug action are not well understood."

Tate Thigpen, director of oncology at the Univ. of Mississippi Medical Center and vice chairman for science of the Gynecologic Oncology Group, reported at last month's meeting of the American Society of Clinical Oncology on GOG's phase 2 study of taxol.

Of 41 evaluable patients with ovarian carcinoma who had relapsed, there were 15 remissions, five of them complete. Eight of the remissions were among the 27 women who were clearly resistant to cisplatin.

Thigpen said GOG next will test the combination of cisplatin and taxol.

"The big problem is with supply," DCT Director Bruce Chabner said. "We would have to deforest the entire Northwest" to get enough of the drug to meet the potential need. So far, efforts to synthesize it have not been successful. Taxol is derived from the bark of the western yew tree (taxus brevifolia), which grows in the Northwest and Canada.

Chabner revealed that NCI will sign a cooperative research and development agreement (CRADA) with Bristol-Myers Squibb for commercial development of taxol. He added that it appears possible that successful synthesis may be achieved using precursors found in abundance in the leaves of the tree.

Chabner said that NCI has enough taxol for current phase 2 studies, and plans to get the drug approved for Group C distribution (free to qualified physicians for patients not on clinical trials).

Michael Grever, acting director of DCT's Developmental Therapeutics Program, said that the rFA will not have an impact on the immediate supply. "If we

THE CANCER LETTER

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ISSN 096-3917. Published 48 times a year by The Cancer Letter Inc., also publisher of The Clinical Cancer Letter and AIDS Update.

treat all 12,000 women who die of ovarian cancer, we would need 20 kilograms a year. This is a major supply problem. If it turns positive for other tumors, even the pharmaceutical industry couldn't handle it."

NCI will hold a conference on all aspects of the development of taxol June 26. Those wishing to attend may phone Matt Suffness, DTP, 301/496-8783.

The concept statement:

The intention of this RFA is to encourage investigators to propose ideas which will increase our knowledge of taxol's properties and which are likely in the long term to contribute to drug supply and to maximally effective usage of taxol in the clinical setting. The following are undeveloped or underdeveloped areas that merit particular interest and attention: (1) total chemical synthesis; (2)biosynthesis and its regulation in taxus species; (3) plant tissue culture to produce taxol and related compounds; (4) agronomics and plant genetics of taxol to enhance production; (5) evaluation of genetic engineering methods to transfer genes involved in taxol biosynthesis to fast growing plants; (6) identification of the specific taxol binding site on microtubules and of the amino acid sequences involved, leading to high resolution definition of the binding site and eventually to molecular mimics with simpler structures; (7) frequency, mechanisms, and circumvention of resistance; (8) studies of in vitro combinations of taxol with other cytotoxic agents; (9) human metabolism of taxol; (1) measurements and consequences of tissue distribution of taxol; and (11) in vivo evaluation of combination therapy using taxol in preclinical models.

In general, studies in the above areas will require relatively small amounts of taxol, which NCI can provide from material that does not meet government manufacturing procedures standards. Thus, awards of grants under this RFA will not compete with clinical trials for taxol.

The Radiation Research Program and the Cancer Therapy Evaluation Program each received concept approval for small grants (RO3) RFAs. These are intended to support correlative laboratory studies of one to two years, with a maximum award of $50,000 a year.

The CTEP RFA will be a reissuance of one earlier this year which generated 162 applications, of which NCI was able to fund only 10. CTEP Director Michael Friedman and his staff were so impressed by the quality and enthusiasm of the applicants that they decided to double the number awarded in FY 1991, provided the NCI budget is such that the money will be available.

The Radiation Research Program was left out of the small grants program earlier this year, when CTEP and DTP initiated their efforts. "That was a mistake," Chabner said.

"We saw a lot of meritorious ideas," Friedman said to Antoine. "I'm very confident you will get some very good applictions. This is a great mechanism to fill a little niche."

The concept statements:

Small grants to stimulate correlative laboratory studies and innovative clinical trials in radiation oncology. Ten awards, one to two years, $800,000 a year (awards will be limited to $50,000 a year in direct costs; the additional amount in the set aside covers anticipated indirect costs).

This RFA is intended to provide a mechanism to foster collaborative interactions between radiation research laboratory scientists and clinicians to support innovative laboratory studies that are related to clinical trials and innovative clinical trials that may require laboratory support. The small grants mechanism (RO3) was selected because of the rapid review and funding that is possible, the relatively modest incremental cost to obtain laboratory studies on patients being treated on clinical trials and correlate the laboratory results with clinical outcome, and the narrow focus of the specific aims in these studies.

This project will fund single or multiple institutions (e.g., individual institutions, consortia, cancer centers, cooperative groups) to perform innovative correlative studies of relevance to clinical trials. Support will be limited to institutions with established clinical, laboratory, and statistical resources that are funded primarily through other sources. These pre-existing resources need not be at a single institution, but may exist within a consortium. Research emphasis should be on, but not limited to, molecular biology and genetic mechaisms, pharmacologic interactions, and radiation resistance. The proposed laboratory studies must have been piloted, preferably extensively, in the proposing laboratory and have been demonstrated applicable to samples of tissue or body fluids, etc., from patients entered onto clinical trials. Statistical support should be included to ensure proper correlation of assay parameters with clinical outcome. Some examples of support that would qualify under this RFA would be salary for an additional technician; money for additional supplies for the assay(s); and salary support for data management, data entry, and coordination of sample procurement.

Small grants to stimulate correlative laboratory studies and innovative clinical trials. Twenty awards, one to two years each, total annual cost $1.6 million. The RFA will be released in July and December, with half the funds to be committed with each round.

It continues to be difficult and time consuming for investigators who propose correlative laboratory studies to clinical trials to obtain complementary funding through either the traditional basic research grant mechanism or the cooperative agreement mechanism. The purpose of this RFA is to provide a continuing mechanism for NCI to foster collaborative interactions between laboratory scientists and clinicians to support innovative laboratory studies that are related to clinical trials, and innovative clinical trials that may require laboratory support.

(The rest of this concept is identical to the last paragraph of the RRP concept).

Study of the clinical pharmacokinetics of anticancer drugs. Recompetition of a contract held by Ohio State Univ. Estimated annual amount, $158,000, five years.

The principal objective of this contract is to provide pharmacokinetic data on new and established antitumor agents used either as single agents or in combination in patients undergoing treatment of malignant disease during phase 1, 2, or 3 studies. The data are to be analyzed for individual variability that can be correlated with clinical response or some other pharmacologic or physiologic parameter, including toxicity. Specifically, these studies will be primarily concerned with the measurement of drug and/or metabolite levels in the plasma with time (ug/ml x min) after a standard dose of the drug. Apparent volume of distribution and plasma protein binding should be

determined.

These studies may also require measurement of urinary, biliary, and fecal excretion of drug and/or metabolites.Measurement of other fluids (e.g. cerebrospinal fluid) and tissues may be necessary. The contractor should have the necessary expertise to develop analytical methodologies for new and established agents; serve as a resource to phase 1 contractors in resolving problems with the methodology, application, and any discrepancies; and assay samples from studies by other institutions with special clinical capabilities and/or samples requiring specific analytical expertise.

The current contractor developed sensitive and selective HPLC assays for quantitating the concentrations of nafidimide, merbarone, ipomeanol, fazarabine, buthionine sulfoximine, melphalan, and pyrazine diazohydroxide and their respecive metabolites in the plasma and urine of patients treated with these gents. In addition, the contractor developed and validated a sensitive and selective HPLC assay for suramin and provided this simplified analytical method to each clinical investigator with an approved phase 2 protocol involving suramin. Each investigator's assay for suramin was then validated by the contractor prior to the initiation of the study. Samples from a flavone acetic acid/IL-2 study being conducted at another institution were also analyzed.

In the future, a great many studies will need to be carried out. We will continue to require more flexibility than is available through the present phase 1 contract mechanism which, by necessity, employs a relatively rigid protocol. This will allow for more in depth studies on the metabolism of each agent. These studies may involve combinations of established anticancer agents to determine the appropriate dose and schedule to limit toxicities and to maximize activity. The contractor should be capable of serving as a resource to assay samples from studies performed at other institutions and to validate assays for outside institutions. In addition, the contractor should be involved in developing the concept of pharmacokinetic guided dose escalation studies and have the expertise to assay the more complex natural products being developed by the division.

The principal investigator of this contract resigned from Ohio State May 1. The CTEP Contract Review Group determined that the contract should be continued for one additional year at reduced funding and then be recompeted.

NCI/DCT Advisors Approve Concept For $15 Million Lymphoma Studies

A $15 million, five year project for grants to support innovative correlative laboratory studies relevant to AIDS related lymphoma clinical trials received concept approval last week from the Board of Scientific Counselors of the Div. of Cancer Treatment.

The approval was one of eight voted by the board involving new or recompeting grant and contract supported projects in DCT's AIDS therapeutic development activities with an estimated total cost of $22.4 million.

The lymphoma study is one of five approved by the board which involves research and/or development in both cancer and AIDS activities. The board also approved other contract concepts, including two recompetitions, which are for AIDS R&D alone. Those will be supported entirely from NCI's allotment of AIDS money; those determined to support both cancer and AIDS activities will be paid for out of both cancer and AIDS funds.

NCI's decision to commit significant resources to treatment of AIDS related lymphoma was based on "a dramatic increase" in the incidence of non-Hodgkin's lymphoma in 20-49 year old men, Cancer Therapy Evaluation Program Director Michael Friedman said. Survival of those patients treated with the various chemotherapeutic regimens developed to treat lymphomas not associated with AIDS "is dreadful," he added.

Some of those regimens have produced remarkable, long term remissions and probably many cures in NHL. They include (regimen acronyms by drug name) CVP, CHOP, COMP, BACOP, M-BACOD, COMLAX, AND PRO-MACE/MOPP. When those have been tested for treatment of AIDS associated NHL, 50 percent response rates have been seen but relapse rates are very high, Friedman said.

CTEP's description of the project in the concept statement:

Adult and pediatric AIDS patients are surviving longer due to improved retroviral and opportunistic infection treatment and care. As a result, AIDS associated malignancies have become more prevalent and are now a major concern.

Lymphomas and Kaposi's sarcomas are the malignancies most frequently seen in AIDS patients. Both non-Hodgkin's lymphoma and Hodgkin's disease have been described in these patients. The etiology of NHL in AIDS patients remains unclear. The most prominent clinical feature of NHL in HIV positive patients is the presence of unusual extralymphatic disease in sites such as the CNS or bowel. Results of treatment using standard intensive multiagent chemotherapy have been disappointing, with median survival of less than one year in treated patients, and difficult because conventional aggressive combination chemotherapy exacerbates the patients' immunodeficient state.

The choice of therapy must be based on the nature of the disease and the overall condition of the patient. The precise relationship of Hodgkin's disease to the underlying immunodeficient state in patients with HIV infection also remains unclear. Clinical observations suggest that Hodgkin;s disease in this setting may have a different natural history and therapeutic outcome when compared with Hodgkin's disease in the general population. Patients with HIV infection and Hodgkin's disease are likely to have a poor therapeutic outcome and to develop AIDS associated opportunistic infections during therapy.

The purpose of this RFA will be to foster collaborative interactions between laboratory scientists and clinicians to devise more effective therapies for the treatment and management of AIDS-lymphoma. Laboratory research efforts and novel therapies ready to be applied in clinical situations and innovative clinical trials are solicited. It is hoped that the results obtained from studying AIDS-lymphoma patients will increase understanding of the biology of lymphomas and will assist in the development of more effective treatment in the general population of lymphoma patients.

This project will fund single or multiple institutions (individual institutions, consortia, cancer centers, etc.) to perform innovative

correlative laboratory studies of relevance to new or ongoing AIDS-lymphoma clinical trials. Eight to 10 awards will be made. Support will be provided to institutions with established clinical, laboratory, and statistical resources. Both adult and pediatric studies are encouraged. Only mature correlative laboratory research efforts that are ready to be applied in clinical situations or innovative new clinical trials for AIDS-lymphoma will be provided support.

Some examples of clinical studies and their correlative laboratory studies that would qualify are:

1. Pharmacokinetic and pharmacodynamic measurements leading to novel means of combining retroviral and antitumor therapies.

2. Biological response modifiers in combination with cytotoxic and radiation therapy, with immune function studies.

3. Bone marrow transplantation, with correlative studies on the transplanted marrow and its progenies.

4. Radiolabeled or toxin conjugated monoclonal antibodies directed against tumor specific antigens with immunotyping as the laboratory correlate.

5. Molecular characterization of oncogenes and growth factors for the development of new antigrowth factor or antisense therapies."

Michael Friedman, director of the Cancer Therapy Evaluation Program, said that the National Institute of Allergy & Infectious Diseases did not have any similar studies under way, and that nothing along those lines was being done in the AIDS Treatment Evaluation Units which NIAID supports.

"Dr. (Anthony) Fauci (NIAID director) and Dr. (Samuel) Broder (NCI director) have discussed the project. It is not CTEP's intention to get involved in anti-infective therapy. That is being handled very well by NIAID," Friedman said.

Board member Paul Carbone, who is chairman of the Eastern Cooperative Oncology Group, said that the cooperative groups might be interested in the problem. He added, however, that AIDS activists and patients "don't like controls," a feature of most cooperative group phase 3 trials.

Friedman pointed out that AIDS-lymphomas progress fast enough that "if you have something that is effective, you will see the impact very soon. Certainly you will need controlled trials later."

Board member Yung-chi Cheng suggested that investigators "take a close look at the etiology of these cancers. Some AIDS therapy may be carcinogenic."

Board member Emil Frei, citing the short duration of responses to existing lymphoma therapy, asked, "Do we know if these are the same lymphomas coming back?" Friedman said that that would be one of the questions to be studied.

"The thrust of these studies should be etiology and pathology, and questions such as (Frei's)."

DCT Director Bruce Chabner said that the NCI Div. of Cancer Etiology is planning to issue an RFA on the etiology and pathology of AIDS-lymphoma which will also earmark $3 million a year for five years.

Carbone suggested that numbers of patients available for the trials might be too small to provide adequate accrual to 10 trials. Friedman disagreed, contending that there are six to nine locations around the country where sufficient numbers of patients are available.

Board members suggested that the RFA be written to emphasize biology, and they approved the initiative unanimously with the understanding it would.

The entire $15 million earmarked for the project will come from NCI's allotment of AIDS funds.

The board approved the concept for a new contract involving both AIDS and cancer programs.

Development of novel drug formulation and delivery systems for antitumor and anti-AIDS agents. One three year contract, estimated cost $250,000 a year.

Potential new therapeutic entities are currently being identified by in vitro screens for development as antitumor and anti-AIDS agents. Many of the substances that have been identified as active are either extremely insoluble or unstable. The composition of these substances represents a broad range of chemical, biological, and natural products. Several approaches such as mixed solvent systems, emulsions, specific salt and micellar formation are used for the formulation of some of these substances. However, certain compounds may not be formulated by these approaches.

The drug substances that are not formulated cannot be evaluated in preclinical toxicology and pharmacology studies and, consequently, will not be evaluated for activity in clinical trials. More exotic delivery systems have been reported, which may prove useful for formulating these compounds. Other delivery systems may also be able to target drug delivery to the diseased tissues. Examples of these novel approaches include intravenous suspensions, attachment of drugs to site directed carriers, cyclodextrin complexes and coacervates for solubilizing drugs, and liposomal encapsulation of drugs. Often the expertise for the development and application of each of these approaches resides with specialty companies and specific individuals. Currently, there is no mechanism in place to support the development of drug formulations using these potential resources.

A substantial effort is required to develop novel drug delivery systems. Currently, the development of formulations of anticancer and anti-AIDS compounds has relied heavily on proven approaches. Although several novel approaches have been developed by existing contractors, new drug delivery systems under development by several research groups may prove valuable for the formulation of drugs for intravenous use. NCI has indirectly supported the development of these delivery systems through Small Business Innovative Research efforts and drug suppliers. Specific compounds have also been formulated using these approaches. Since these approaches have not been generally applicable to a wide number of compounds and the time required for development of a new formulation can be substantial, existing formulation contracts have directed efforts toward more proven approaches. However, if progress in this area is to continue and we are to be associated with the application of these approaches, financial support for these studies will be required. For this reason, a task order managed mechanism for funding the development of specific formulations of new anticancer and anti-AIDS drugs is desired.

The research organizations must be highly qualified and experienced in pharmaceutical development and must possess adequate instrumentation and capabilities to evaluate the integrity of the systems developed.

The formulation must be adaptable to the intravenous or oral delivery of drugs to patients and must meet the usual requirements for the type of pharmaceutical dosage form developed. The novel approaches may also be used to develop alternative intravenous vehicle systems to reduce irritation at the delivery site for existing drugs. Upon acceptance of the delivery system, a preclinical toxicologic assessment will be made by NCI, and all necessary documentation will be filed with FDA for clinical trials.

The primary purpose of this procurement is to provide additional resources for the development of formulations of anticancer and anti-AIDS drugs. The use of pharmaceutical groups that specialize in novel drug delivery systems may result in production of superior formulations to those which could be obtained using conventional methods. The results obtained from this effort will be important for the further development of drug formulation and drug delivery research. The development of novel drug delivery systems may also provide important therapeutic advances for existing anticancer and anti-AIDS drugs.

The board approved recompetition of two existing contracts which will serve both AIDS and cancer investigtions.

Collection and taxonomy of shallow water marine organisms. Recompetition of contracts held by Harbor Branch Oceanographic Institute and Australian Institute of Marine Science. SeaPharm Inc. was an original contractor on this project but that firm went out of business two years ago. Depending on proposals received, multiple contracts may be awarded for five years, with estimated total cost of $578,000 a year.

The marine environment is a tremendously varied and rich habitat which, relative to plans and microbes, has been little explored as a source of drugs. Over one half of the phyla of the animal kingdom are recognized as being exclusively marine, and it is readily apparent from the literature in the marine natural products field that the chemical types of the secondary metabolites produced are quite different from those of the terrestrial plans, animals, and microbes.

Because 98 percent of the ocean is a nutrient poor desert, marine life congregates in the nutrient rich areas near land, and there is an intense competition for food and living space, which is a kind of chemical warfare among species, involving the production of a wide variety of offensive and defensive toxins, repellents, attractants, and camouflages. The production of so many biologically active compounds, many designed to kill or incapacitate other species and some to promote growth, speaks well for the likelihood of discovering compounds with antitumor and antiviral activity.

Approximately 15,000 marine organism extracts were screened for antitumor activity in the earlier NCI program, and even fewer have been screened for antiviral activity. The extracts originally screened by NCI were mainly provided by independent research groups involved in the study of marine natural products chemistry, but, prior to the award of the collection contract to SeaPharm Inc., in September, 1986, NCI had not been directly involved in large scale collections. SeaPharm held the contract until April, 1988, when it was terminated due to a declaration of bankruptcy by the company. Harbor Branch Oceanographic Institute, which had aided SeaPharm in various aspects of the collection program, continued the operation for 14 months, at which stage a new two year contract was awarded to the Australian Institute of Marine Sciences in Townsville, Queensland.

Collections of 1,000 organisms per year are currently focused in the Indo-Pacific region. Samples of approximately 1 kg are drained and frozen immediately on removal from the water, and are shipped frozen by air freight to the Natural Products Laboratory in the Frederick Cancer Research Center, Maryland, where they are stored at -20 degrees C. The frozen samples are ground with dry ice, water added, and the mixture centrifuged to give an aqueous extract. The solid residue is then extracted with an organic solvent. The extracts are returned to the repository for low temperature storage.

As screening capacity becomes available, small samples of each extract are tested for AIDS-antiviral and antitumor activity. When significant activity is observed, bulk extracts are subjected to bioassay guided fractionation with a view to isolating the active components. When necessary, large scale recollections of active organisms are undertaken to provide sufficient material for further development.

The collections are primarily of invertebrate organisms, with a focus being on classes of organisms known to produce novel bioactive chemotypes, such as sponges and tunicates. Voucher specimens of each species are prepared using established preservation techniques, and specimens are deposited with local repositories in collection countries and the Smithsonian Oceanographic Sorting Center of the Museum of Natural History. Taxonomic identification down to species level (where possible) is required, and detailed records of date and location of collection, physical characteristics, habitat and photography (underwater and surface) are submitted for each species collected.

Up to February, 1990, over 3,500 samples from 19 different phyla representing 175 orders and 1,150 genera had been collected. Extensive studies to determine the optimum method of extraction using known bioactive species were undertaken resulting in a considerable delay in the start of routine extraction; as of February, 1,536 extracts have been prepared.

Of 965 extracts submitted for AIDS-antiviral testing, 92 extracts of marine invertebrates have exhibited preliminary in vitro activity. In addition, 136 aqueous extracts of marine algae have shown activity, but these are known to contain carrageenan sulfates which, like dextran sulfate, possess marked in vitro activity. A dereplication method to determine the occurrence of such sulfated polysaccharides has been developed. Over 27 of the active invertebrate extracts are in various stages of fractionation.

While the species rich Indo-Pacific region is still favored as the prime collection area, consideration will be given to proposed collections in other regions, provided adequate justification for selection of such regions is furnished. The number of species collected during the current five year contract period will be approximately 5,000 which represents a small fraction of those occurring in tropical waters. The potential for new drug discovery from marine organisms thus remains extremely high.

The new contracts will be supported entirely with NCI AIDS money despite the fact that the effort will continue to collect potential anticancer agents along with anti-AIDS/antiviral organisms. Michael Grever, acting director of the Developmental Therapeutics Program, explained that the existing contracts were paid entirely from cancer funds, "although most of the organisms coming out now are potential anti-AIDS. We think it is fair that AIDS money for it this time."

Board member Phillip Crews suggested that the agents in the repository should be made available to the drug discovery groups and other investigators.

Grever said that a committee is being established which will review proposals from the groups and others requesting agents from the repository. "We need to do it carefully so the repository will not be inadvertently depleted."

Computer based searches for chemical structures. Recompetition of a contract held by Z Inc. Five years, estimated annual cost, $115,000. This will probably be a small business set aside.

The contractor performs high volume computerized chemical structure searches, generates chemical abstracts service index names, and searches and obtains scientific articles and patents in response to requests from the drug Synthesis & Chemistry Branch, Natural Products Branch, and National Cooperative Drug Discovery Groups.

During the past year, the contractor processed more than 350 chemical structure queries. About 60 percent of those searches were run against DIS, and the remaining were run against STN, DIALOG, and NLM/MEDLAR systems. Systematic names for more than 100 compounds were generated. Also, more than 275 searches of scientific articles and patents were performed. In recent months, the contractor has also been involved in bibliographic searches in support of the natural product programs.

With the initiation of the new cancer screens, there will be a continuing need for high volume chemical searches as mentioned above to support various segments of DTP, namely, DS&CB, NPB, and NCDDG. The task requirements will be advertised essentially as presently documented. Since the contractor is equally involved in both the cancer and AIDS drug discovery efforts, 50 percent of the funds will be derived from each of the two programs.

Grever said that DTP had considered doing this work in house but that "we determined it couldn't be done any cheaper or as efficiently." He added the information is available to drug discovery groups and that efforts would be made to inform them of that.

NCI has contracts for collection of natural products with potential for anticancer and antiviral activity in 25 countries, including 13 in Latin America and the Caribbean. However, a notable exception has been Brazil, which does not permit the export of plant material for chemical examination and drug development. NCI staff members have regretted the absence of the major portion of the Amazon rain forest which lies in Brazil from the program.

In a recent development, Brazilian scientists have formed Fundacao Brasileira de Plantas Medicinais, whose primary goal is study of potential Brazilian medicinal plans as sources of new drugs. The organization has agreed to supply potential anticancer and antiviral plant extracts to NCI.

The board approved reprogramming of $150,000 a year for three years from existing contracts to a sole source contract with the Brazilian organization. This will provide up to 1,500 plant extracts for testing in the NCI anticancer and antiviral screens. It will result in reduction by 20 percent of the plant samples collected by the other contractors.

The concepts approved which involve only AIDS activities were:

--Dosage form development of new agents for the treatment of AIDS. Three years, estimated annual cost $250,000, a new contract.

--Recompetition of a contract held by Southern Research Institute for detailed drug evaluation of anti-AIDS agents, estimated annual cost, $500,000, three years.

--Recompetition of a contract held by the Medical Illness Counseling Center for neuropsychological testing for children and adults with HIV infection. Estimated annual cost, $250,000, two years.

Detailed descriptions of the AIDS only concepts were reported in the June 8 issue of **AIDS update.**

Broder: Is It "Downward Negotiations" Or Coercion? Defends NCI Authority

The NCI director was having a dialogue with members of the American Society of Clinical Oncology at their recent annual meeting in Washington DC. The inevitable subject of NCI's inadequate budget was one of the topics under discussion.

"I'm worried about the effect on institutions of downward negotiations," Samuel Broder said, using the current federal euphemism for "we're cutting your grant."

"There is no negotiation involved," Broder continued. "The negotiation is as follows: We say, 'Your grant is going to be cut 20 percent. Do you accept?' If that is negotiation, I don't want to hear anything about coercion."

ASCO member James Holland referred to speculation from some quarters that one of the reasons why the Administration has had so much difficulty in finding a new NIH director is the independent authorities granted the NCI director by the National Cancer Act. "We certainly would not look with favor on changing those," Holland said.

Neither would Broder. "If they remove the special authorities of NCI, they might have trouble getting an NCI director," he said.

Broder said he blamed the failure to find someone to lead NIH in a year long search "on those responsible for doing the recruiting.

"Of course, the salary they can offer an NIH director has nothing to do with it," he said with more

than a touch of sarcasm. "Neither does the litmus test [a candidate's view of fetal research], or mandatory urinalysis. The special authorities of NCI does not have anything to do with recruiting an NIH director."

Sullivan Charges Tobacco Industry With "Lies, Blue Smoke, Mirrors"

It is clear now that Louis Sullivan has declared war on the tobacco industry.

A few weeks after the secretary of the Dept. of Health & Human Services had jawboned the industry into abandoning an effort to target blacks in an advertising blitz for a new cigarette, Sullivan addressed the American Assn. for Cancer Research at its annual meeting and bitterly attacked the industry for perpetuating "lies. . . blue smoke, mirrors, misleading suggestions and clever distractions."

Sullivan called on the advertising and publishing industries to reject the "blood money offered by the tobacco industry. It seems obvious that any ethical approach to business would factor the source of the money and the consequences of the use of the products advertisers urge the public to use."

The arguments stated by those who continue to deal with tobacco advertising and promotion, that "business is business, is an attitude I find intolerable," Sullivan said. "There must come a time when enough people have died, when we have had enough funerals and grieving relatives and personal tragedy. There must come a time when passive smokers, and those who foot the bill for the cost of smoking, must forcefully voice their own opinions. There must be a time when we ask the advertising industry to harness its creative talents in the promotion of health, not the promotion of illness. There must be a limit to what we will allow, and I believe that we have reached that limit."

Sullivan's address was interrupted by a demonstration by members of AIDS Coalition to Unleash Power, the organization which earlier in the week had demonstrated at NIH. The half dozen who eluded guards and slipped into the AACR meeting hall were orderly, called on Sullivan to remove HIV from the list of immigration restrictions, take other actions promoted by ACT UP, and "appoint an NIH director."

Most of those actions are in the hands of the White House or Congress rather than the HHS secretary. Sullivan responded by the demonstrations were against "the one part of the government most concerned and sympathetic to AIDS victims. All of us want to end this scourge. It is understandable that these people are upset. But I resent the accusations and disruptions from groups such as this. We will continue doing everything possible to work against AIDS."

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 Executive Plaza South room number shown, National Cancer Institute, Bethesda MD 20892. Proposals may be hand delivered to the Executive Plaza South Building, 6130 Executive Blvd., Rockville MD. RFP announcements from other agencies will include the complete mailing address at the end of each.

NCI CP-05652-51

Title: Transplacental carcinogenesis and tumor promotion in Old World monkeys

Deadline: Approximately July 31

NCI has a requirement for a contractor to provide continued studies of transplacental carcinogenesis and tumor promotion in nonhuman primates in support of the intramural research program of the Laboratory of Comparative Carcinogenesis. This contract will provide for animal facilities adequate to house approximately 185 monkeys, all to be patas (Erythrocebus patas), or up to approximately 100 cynomolgus monkeys (Macaca fascicularis) or other compatible species in place of an equal number of patas in cages that shall be provided by the contractor.

Technical assistance in the form of carcinogen or tumor promotor administration to animals, monitoring the animals for enzootic diseases and for tumor development, collection of biological samples from animals, administration of medication where appropriate, maintenance of records, performing surgical procedures and assistance in necropsy of animals will be provided by the contractor. This acquisition is a recompetition of a previous contract and is anticipated to cover a five year period.

Contract Specialist: Chris Ptak
RCB Executive Plaza South Rm 620
301/496-8611

NCI CP-05651

Title: Laboratory rodent and rabbit facility for the Laboratory of Cellular Carcinogenesis and Tumor Promotion

Deadline: Approximately July 20

NCI has a requirement for a contractor to provide facilities and staff to house, care for and conduct experiments with laboratory rodents and rabbits as directed by protocols from NCI investigators. The numbers of animals for which facilities shall be provided will vary with current program needs, but facilities to house the following numbers of rodents are required: 1,000 athymic mice, 3,700 intact mice, 300 transgenic mice, 50 rabbits, 200 hamsters, 150 rats, 20 guinea pigs. Animals will be purchased by NCI, not the contractor. This acquisition is to support the Intramural Research Program of the laboratory of Cellular Carcinogenesis and Tumor Promotion, located in Bethesda, MD, and respondents must be able to accomplish a frequent exchange of animals and fresh specimens and injectable call suspensions with the LCCTP. This acquisition is a recompetition and one award is anticipated to cover a four year period. The proposed contract is a 100 percent small business set aside.

Contract Specialist: Chris Ptak
RCB Executive Plaza South Rm 620
301/496-8611