THE CANCER LETTER

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NCI Plans Trials Of Burzynski's 'Antineoplaston'; JAMA Report Says No Antitumor Activity In Tests

NCI plans to conduct four phase 2 trials of "antineoplaston," a controversial substance invented by the Polish-trained physician Stanislaw Burzynski and available only at a Texas clinic that has been the target of regulatory and disciplinary actions by state and federal authorities.

Even before NCI's Cancer Therapy Evaluation Program sent out its

(Continued to page 2)

In Brief

Cancer Center Scientist Set For Space Launch; NIH Star French Anderson Negotiating With USC

LARRY DELUCAS, Univ. of Alabama at Birmingham Comprehensive Cancer Center, will be launched into space June 17 on the NASA shuttle Columbia to crystalize 32 human proteins in 736 experiments over 13 days. DeLucas competed with three other scientists for the spot as payload specialist for NASA's "Microgravity Laboratory" mission. DeLucas has worked with NASA for several years attempting to train astronauts to conduct crystallography experiments. On the same day, the center will dedicate its three-story addition to the Wallace Tumor Institute. NCI Director **Samuel Broder** and American Cancer Society President **Walter Lawrence** are scheduled to attend the event. . . . **FRENCH ANDERSON**, gene therapy pioneer at the National Heart, Lung & Blood Institute, told his staff he may leave NIH and is negotiating with Univ. of Southern California. Anderson intends to follow his wife, Kathryn Anderson, acting surgery chief at Children's National Medical Center and leading contender for the surgeon-in-chief job at Children's Hospital of Los Angeles. . . . **BRIAN HENDERSON**, director of the Kenneth Norris Comprehensive Cancer Center, Univ. of Southern California, has been elected to the National Academy of Sciences. Henderson, an epidemiologist, is the first scientist from the center and the fifth from USC to receive the recognition. . . . **MICHAEL MARTIN** was appointed deputy associate director for program activities, National Institute of General Medical Sciences. Martin was program director for basic cancer biology in the Cancer Biology Branch, NCI Div. of Biology, Diagnosis & Centers. . . . **ERIC ROSENTHAL**, Fox Chase Cancer Center, was elected to a third term as chairman of the Public Affairs Network of 57 NCI designated cancer centers. **Dianne Shaw**, Lineberger Comprehensive Cancer Center, was elected vice chairman. New steering committee members: **Jan Barkley**, Lombardi Cancer Research Center; **Jeannie Frieden**, Institute for Cancer Research & Care; and **Laurie Young**, Arizona Cancer Center.

Pediatric Oncologists Oppose Trial Of Burzynski's Antineoplaston

(Continued from page 1)
request to clinical investigators for letters of intent to conduct three separate trials in adults and one trial in children with glioblastoma and astrocytoma, a number of pediatric oncologists wrote to NCI that they opposed the trial.

Instead of the requested letter of intent, Henry Friedman, Duke Univ. professor of pediatric oncology, submitted a piece of correspondence he called "A Letter of No Intent."

"The problem I have with antineoplaston in adult tumors is that I am not convinced that the data justifies the study," Friedman, who is also the chairman of the brain tumor core committee of the Pediatric Oncology Group, said to **The Cancer Letter.** "Further, no pediatric studies should commence until phase 1 adult studies have been conducted."

Another critic of the trial, Jonathan Finlay, vice chairman of the Dept. of Pediatrics at Memorial Sloan-Kettering Cancer Center and former chairman of the brain tumor strategy group of the Children's Cancer Study Group, wrote in a letter to NCI:

"Some of my pediatric neurooncology colleagues who cared for children with brain tumors treated at one time or another with antineoplaston therapies have expressed concerns about possible non-neurologic as well as neurologic toxicities of antineoplastons. Until these toxicities--or lack of them--can be demonstrated within the adult brain tumor population, I do not feel that it would be appropriate to initiate or encourage any NCI sponsored trials in childhood brain tumor patients."

The Cancer Letter was unable to learn how many letters of intent NCI received by the Institute's deadline June 1.

THE CANCER LETTER

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On June 3, the "Journal of the American Medical Assn." published a peer reviewed paper analyzing the scientific claims for antineoplastons, which are described by their inventor as urinary peptides capable of "reprogramming" cancer cells.

According to the JAMA paper by Saul Green, a retired Memorial Sloan-Kettering biochemist, "a treatment for cancer with the substances called antineoplastons actually involves two simple organic chemicals [available] under the names of A-10, AS 2.1 and AS 2.5. None of these substances is a peptide, none has been shown to 'normalize' tumor cells, none has been shown to intercalate DNA, and none has been proven to be active against cancer in experimental tumor test systems."

Congressional Mandate

"Our threshold for doing this has been lowered by a serious instruction from Congress," Bruce Chabner, Director of NCI's Div. of Cancer Treatment, said to **The Cancer Letter.** In fiscal 1992, Congress provided $2 million for NIH to establish an office that would "test the most promising unconventional medical practices." The antineoplaston trial is the first to be conducted under this Congressional mandate, Chabner said.

"We realize that this stuff is very controversial and in the academic community there is a high index of skepticism attached to the drug," he said.

However, commenting on the JAMA paper, Chabner said. "I don't think [Green's] conclusion that none of these compounds are shown to be active is accurate. A number of papers have shown evidence of some antineoplastic activity. Some very capable oncologists have reviewed the substance and they believe that in the best cases there is some evidence of activity."

Basic research at NIH involving antineoplaston has been conducted by Dvorit Samid and Charles Myers. An article by Hideaki Tsuda in the May issue of the "Japanese Journal of Cancer Research" reports some activity of the agent.

"I think there is a significant potential downside for Dr. Burzynski here," Chabner said. "This trial could put his operation out of business if his agent doesn't work. That's not our purpose in doing this trial, but if that happens, so be it. That's what happens to inactive drugs."

Over the years NCI has evaluated a number of unconventional therapies, including laetrile, vitamin c and hydrazine sulphate. "We have to be ready to evaluate anything that holds promise, even if the data are slim," said CTEP Director Michael Friedman.

"We are inviting people to send us their best case series, and if on review there is an association

between antitumor effect and an agent, we will pursue the trials," Friedman said. "In the past, these agents have been mostly negative, but that does not mean that this one will not be positive."

Whatever the outcome, the "letters of no intent" as well as the uncanny timing of the JAMA paper have put a new emphasis on the controversy that has been shaping for well over a decade.

Now, meet its principal actors:

Burzynski, the inventor of the agent, who says that cancer is the result of deficiency in peptides. Cancer can be cured if peptides are supplied to the patient, Burzynski says.

Michael Hawkins, the outgoing chief of DCT's Investigational Drugs Branch, who was involved in the NCI decision to conduct a trial of Burzynski's agent. Hawkins, who is leaving NCI for Georgetown Univ., was on vacation and an attempt to reach him was unsuccessful.

David Parkinson, the newly appointed acting branch chief, will be acting under the same mandate, Chabner said.

Grace Monaco, a founder of Candlelighters, member of the FDA Oncologic Drugs Advisory Committee and a consultant to an insurance company that has been sued for reimbursement by Burzynski's patient. Burzynski has since sued the insurer and Monaco personally.

Green, the biochemist who wrote the JAMA paper, has been analyzing scientific claims of unconventional therapists in light of traditional science. He has also been a volunteer for Candlelighters and Monaco's consultant on grants and litigation.

"I am not qualified to evaluate Burzynski's clinical claims,'" Green said to **The Cancer Letter.** "But I can say that the scientific basis he describes in his publications isn't valid. His agents have never been shown to do what he says they do and two of the materials he administers as treatment become the same substance in the body."

"Ammo for Docs..."

Green said that the timing of his paper's publication was accidental. It was submitted to JAMA last September.

According to David Cooper, JAMA's contributing editor and director of the Div. of Endocrinology of the Sinai Hospital in Baltimore, the Green paper had been reviewed by five physicians, two of them oncologists, and by one attorney.

"Many physicians don't know how to rebut their patients' arguments when the patient says, 'Doc, I have so many months to live, so why don't I go see Dr. Burzynski or someone like him," Cooper said. "This gives the physician the ammunition to say, 'Here are the facts,' without sounding paternalistic."

A spokesman for Burzynski said that a scientific rebuttal of the JAMA article would be forthcoming.

"It's a scientific article and the only way I want to respond is in scientific terms," Le Trombetta, director of public information for Houston based Burzynski Research Institute, said to **The Cancer Letter.** "We will make a line by line rebuttal once we've had a chance to review the article.

"The goal shared by NCI and BRI is simply the independent clinical testing of Dr. Burzynski's antineoplaston treatment. What possible motive could someone have in opposing these trials? Perhaps the results of these trials could prove to be an embarrassment to those people who have taken such a prominent public stance in their denunciation of Dr. Burzynski.

"We are proceeding with our first priority, which is getting this medication tested independently," Trombetta said.

At this time, BRI staff is supplying documentation on the IND for the trials scheduled to begin in July, she said.

"Simple, Pure Heresy..."

Burzynski's theory on cancer is admittedly far from the mainstream.

"What I am going to tell you today is just simple, pure, heresy," he said in October, 1990, to a sympathetic audience at the World Research Foundation Congress, an unconventional treatment forum.

"Basically what I dare to propose is that the immune system is not everything," Burzynski said. "There is another body defense system which I discovered and named the 'biochemical defense system.'"

Cancer, Burzynski says, is the result of deficiency in peptides he calls "antineoplastons."

"If we supply antineoplastons to these people then, theoretically, we should get rid of cancer and we should be able, also, to prevent cancer.

"It's no longer killing of the cells, but changing the program inside the defective cells, which means that the cells begin to function normally," he said in that lecture. "In the case of cancer, for instance, if all of the cancer cells will be reprogrammed and function normally, then, ultimately, we won't have cancer anymore."

According to his curriculum vitae, Burzynski received an MD at the Medical Academy of Lublin in 1967 and a Ph.D. equivalent degree a year later, following work on isolation of peptides. He came to

the U.S. in 1970 and worked at Baylor Univ. on isolation of peptides from brain tissue and urine. That work was funded by an NCI grant.

In 1973, Burzynski passed an exam to practice medicine in Texas and was named assistant professor at the Dept. of Anesthesiology, where he worked on an NCI grant to perform basic research with peptides in animal models. In 1977, after expiration of the NCI grant, Burzynski left Baylor.

Soon thereafter he started to treat a variety of cancers as well as psoriasis, chronic ulcers and Parkinson's disease. Recently Burzynski began seeing AIDS patients.

"It began with the patient who had both cancer and AIDS at the same time," Burzynski said at the conference. "We started in the beginning of [1990] and we have only one patient who became HIV negative at this time, but most of these patients had marked improvement in their cells." Burzynski continues to see AIDS patients, Trombetta said.

According to a price schedule provided by BRI, charges for a day's therapy range from $135 to $685. The patient also pays for housing, meals and diagnostic procedures. If IV treatment is prescribed, the patient provides a catheter and a pump. "We require an initial $5,000 deposit from patient to start treatment," the price schedule reads. "After the first week of treatment, we will begin filing claims to the patient's insurance carrier."

NCI screened a number of Burzynski's antineoplastons in 1983 and 1990, finding no antitumor effect. According to his attorney, Richard Jaffe of Houston, Burzynski said the Institute used inappropriate screens, which resulted in false-negative results.

Burzynski filed an IND in 1983, but FDA placed the application on clinical hold, which was released six years later, giving Burzynski permission to proceed with a study of 16 refractory stage IV breast cancer patients. According to Trombetta, that trial has not been initiated. "The problem is finding the funding," she said. "This is a clinic of a lone practitioner. We don't have the funds of a pharmaceutical company."

In 1983 a judge in the U.S. District Court for the Southern District of Texas restricted Burzynski from shipping his agents across state lines. In 1986, the Texas Board of Medical Examiners initiated proceedings to revoke Burzynski's license, alleging "administering of a drug or treatment that is nontherapeutic in nature."

The matter has since been referred to the state attorney general's office. The complaint filed by state prosecutors includes allegations that Burzynski failed to order x-rays when they were needed; led a patient's spouse to believe that cancer was arrested, when in fact the chest x-ray was unreadable; prescribed a subtherapeutic dosage of methotrexate and failed to provide irradiation treatment when it was indicated.

The attorney general's office told **The Cancer Letter** that the document is likely to be amended further before action by state prosecutors begins.

Insurance companies, too, have been part of the controversy. In 1986, Kenneth Swanson, the widower of a lung cancer patient treated by Burzynski, sued his insurer, Aetna Life Insurance Co., for reimbursement. Burzynski joined the suit and Aetna countered with a civil suit alleging violations of federal Racketeer Influenced and Corrupt Organizations Act statutes.

It was in that case that Burzynski first clashed with Monaco, who was hired as a consultant by Aetna.

Monaco v. Burzynski; Burzynski v. Monaco

The Monaco-Burzynski clash has not been limited to the courtroom and has reached beyond Swanson v. Aetna.

For years prior to the Burzynski litigation, Monaco assisted patients and consulted insurance companies on reimbursement as well as matters related to cancer treatment technology.

Monaco first became aware of Burzynski in 1977, soon after he started seeing pediatric patients.

"I hoped then and I hope now that he has a product that can help treat brain tumors," Monaco said. "However, the patients have a right to know whether claims for any treatment--standard, investigational or unconventional--are fairly represented to them." In one case, when she consulted for an insurance company that was trying to deny a claim for treatment by another unconventional practitioner, Lawrence Burton of the Bahamas, Monaco called Green, whose article on Burton she had seen in a medical journal.

Green's expertise in unconventional therapy had come the hard way:

After Green published a 1979 paper on tumor necrosis factor, Burton accused him of using his discovery without proper credit, Green said. Green responded by compiling a file on Burton and his scientific claims.

After that case, Green and Monaco collaborated in volunteer review work for Candlelighters as well as in litigation and grant work. In 1987, while the database idea was in planning stages, Monaco was asked by Aetna to act as a consultant to the law firm of Hinshaw and Culbertson of Chicago, the lead firm in the case.

In 1988, Monaco founded a consulting group called Emprise Inc. One of Emprise's projects, funded through $550,000 in Small Business Innovative Research grants from NCI, was to compile the database that would make scientific reviews on unconventional therapies available to physicians, patients and third party payers. Green served as a scientific advisor on the project.

As soon as the work on the database began, Burzynski wrote a letter to NCI director Samuel Broder, alleging that Monaco was compiling the database that would help Aetna in the litigation.

Following that letter and an NCI investigation, the grant remained in force, but Monaco was asked by NCI to suspend her activity on the case, which she did in 1989, Monaco said.

Thus, at different times Monaco found herself confronting Burzynski on three fronts: as a patient rights activist with Candlelighters, as an attorney, and as an NCI grantee managing a database that included an evaluation of antineoplastons.

History of the Case

After Swanson and Burzynski sued Aetna, the insurer countersued, claiming that Burzynski had made fraudulent representations, thereby misleading his patients to pay for useless treatment. This constituted a RICO violation, Aetna claimed.

The case, which originated in Illinois, was ultimately referred to the U.S. District Court for the Southern District of Texas.

On March 31, Judge Kenneth Hoyt ruled that Swanson was not entitled to reimbursement because the treatment was not medically necessary. He also found that the insurance company knew that antineoplaston was an unproven drug, and since there was no "detrimental reliance" on the insurer's part, RICO statutes were not violated.

In a separate suit, Burzynski claimed tortuous interference and interference with a prospective business relationship on the part of Aetna and Monaco's Emprise. That case was resolved in favor of Aetna and Monaco last year. The case is being appealed.

Meanwhile, outside the courtroom, Monaco's database project was crippled by the litigation.

The database had cleared peer review, but as a result of Burzynski's suit, Monaco's business associate in Emprise decided that the company would not be able to distribute the database without obtaining liability coverage, Monaco told **The Cancer Letter.**

"Our little firm couldn't afford the insurance, so we dissolved the business," Monaco said.

Left without a home for the database, Monaco offered to turn it over to NCI.

"Unless it is aggressively maintained, the database will quickly become outdated and incomplete," Hawkins wrote back to her last August.

"We would therefore be willing to accept it only if we were able to keep it at its current high level... Unfortunately, it is difficult for a public institution to exclude any approach from such a database once it exists. Based on these factors, NCI is reluctant to commit the resources that would be required to maintain your database in an adequate fashion. Therefore we do not feel it is appropriate to accept it as a gift.

"NCI is strongly committed to the principle of actively reviewing data that are provided to us by proponents of any therapy--'unconventional' or not," the letter continued. "However, we do not have the resources to seek out data on all therapies and do not have a practical way to limit our involvement."

The NCI Trial

Last October, an NCI team visited Burzynski's clinic, and in early December, Burzynski issued a press release announcing that NCI will conduct four phase 2 trials of his agent.

Having learned about the press release, Monaco asked pediatric cancer specialists around the country to evaluate the appropriateness of the trial in children. Monaco said she was concerned that phase 2 trials were proposed even though phase 1 toxicity trials had not been done. This triggered something of a letter-writing campaign to Hawkins.

Responding to these letters, Hawkins wrote:

"The decision by NCI to conduct independent clinical trials with antineoplastons was based primarily upon a site visit which we conducted in October 1991.

"Dr. Burzynski prepared cases for our review which met the criteria for a 'best case series.' The site visit team which reviewed the cases in question consisted of a neurologist, a neuropathologist, two medical oncologists (one of whom has conducted phase 2 trials in patients with brain tumors), and individuals from Regulatory Affairs Branch.

"They reviewed seven patients who reportedly did not receive concurrent treatment with other modalities and who had proper radiographic studies done before and after the treatment. The neuroradiologist reviewed the actual scans and the pathology slides were reviewed by a neuropathologist.

"While the referring physician of each patient was not contacted independently, there were letters in the patients charts from referring physicians who followed the patients while they were receiving antineoplastons which confirmed the case histories we reviewed.

"Some of these patients were extensively pretreated and, in all cases, it was difficult to attribute the reduction in tumor size to anything other than treatment with antineoplaston. Of note, a number of these patients had previously progressed when given antineoplastons orally and the administration of highly purified product by continuous IV infusion is a relatively recent modification by Dr. Burzynski. It is possible that this change may explain some of the negative audits that have occurred in the past.

"While antineoplastons were first identified as extracts from urine, they were have been chemically well defined and are now manufactured using large scale production facilities...

"The NCI is not taking the position that antineoplastons are active anticancer agents, only that they are worthy of investigation. The CT and MRI scans that the site visit team audited were reviewed by the Div. of Cancer Treatment's Decision Network which agreed that a limited number of phase 2 trials in brain tumors were indicated.

"The NCI has conducted trials with other unconventional therapies (e.g. vitamin C and laetrile) and these data were useful in objectively documenting the lack of activity of these agents.

"If phase 2 trials are negative, interest in antineoplastons would decrease markedly, regardless of any disclaimers by Dr. Burzynski. If the trials are positive, we will have found a novel agent for the treatment of brain tumors and perhaps other malignancies."

The CTEP Letter

According to a CTEP letter to clinical investigators:

"NCI is requesting letters of intent to conduct phase 2 trials of antineoplastons A10 1 gram/kg/day and AS2-1 .5 gram/kg/day administered by continuous IV infusion using programmable pumps until the development of progressive disease. Treatment is primarily outpatient and patients would be instructed in use of the pump for home use. The replacement of the antineoplaston solutions in the pumps would be required every day, and can be done at home. Antineoplastons will be provided free of charge to the NCI by Dr. Burzynski and the studies will be conducted under a DCT IND. All patients would have clearly measurable disease on MRI and have progressed following previous therapy. The case records, MRI scans and pathology slides of any patient who id reported to respond will be reviewed by the Cancer Therapy Evaluation Program. Reported toxicities from antineoplastons have been minimal.

"NCI would like to conduct three separate trials in adult patients with glioblastoma multiforme, anaplastic astrocytoma and low grade astrocytomas and one trial in pediatric patients. The amount of prior therapy, performance status and other eligibility criteria should be similar to those used for other phase 2 trials at your institution in these diseases."

RFPs Available

Requests for proposals described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. 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 NCI-CM-37821-28

Title: In vivo testing--potential sources sought

Deadline: Approximately June 15

The Developmental Therapeutics Program, NCI Div. of Cancer Treatment, is seeking 8(a) and small business sources with SIC Code 8731 who have the necessary experience, scientific and technical personnel and facilities to conduct in vivo testing of compounds that have demonstrated in vitro activity against a battery of human tumor cell lines. Secondary in vivo testing is essential in order to confirm activity of a compound and further define its specificity.

This project may require any or all of the following: direct on-site support at the contractor's facility for in vitro expansion of cell lines; initial in vivo assays utilizing rapid and sensitive procedures; detailed followup in vivo studies; investigation into the effect of formulation treatment schedules, route of drug administration and site of tumor implantation or drug activity. The contractor shall be required to receive, maintain, and experimentally use regular and/or athymic nude mice; propagate and maintain tumor stock in vivo; prepare and administer test materials to tumor bearing or non tumor bearing animals; monitor the quality of all tumor lines and mice; determine test material activity and report the results. The government will provide the compounds to be tested and determine the assay systems to be utilized. Contractors shall be expected to provide all equipment, solvents, reagents and animal facilities needed to conduct this type of work.

The following mandatory qualification criteria will apply: 1) the contractor may not be a pharmaceutical or chemical firm since compounds of a commercially confidential nature may be evaluated, 2) since structural formulas and other information in discreet compounds may be included, contractors must be willing to sing a confidentiality of information statement.

Technical approaches and methodology include the capability to conduct xenograft testing and proficiency in utilization of in vivo models such as subcutaneous, intraperitoneal, subrenal capsule, etc. Tumor tissue to be utilized for this effort may be of several types. Not only will solid tumor fragments be employed, but also ascitic material, brei, or solid tumor digestion. Inoculation of this material IP and experience with tumor staging (employing the types listed above), dosing regimens, etc. in both early and late stage tumor systems should also be documented.

It is expected that two completion type contracts will be awarded. The government considers the following estimated number of assignments will be required per annum: Level A in vivo tests=2500 LOX-IMVI equivalents (12,500 LOX-IMVI equivalents total). Level B in vivo tests=3800 LOX-IMVI equivalents (19,000 LOX-IMVI equivalents total). Responders must submit capability statements to conduct testing at Level A and may submit capability statements to conduct testing at level B. LOX-IMVI equivalents for advanced stage subcutaneous tumor systems will be 2.5 and for subrenal capsule 3.5. Early stage subcutaneous tumor systems are equivalent to one LOX-IMVI test. The total level of effort for the five year period of

performance is estimated to be 42,170 hours for Level A and 63,250 hours for Level B. The personnel should include a principal investigator, other key investigators and any additional personnel.
Contract specialist: Joyce Crooke
RCB Executive Plaza South Rm 603
301/496-8620

RFP NCI-CO-33008-61
Title: Support services for OD, NCI
Deadline: Approximately June 25

This competitive acquisition is to obtain services which support the activities of the Office of the Director, NCI. These support services fall into four major areas: 1) task administration, 2) documentation and presentations, 3) conference and meeting management, 4) on-site typing services.
Contract specialist: Charles Jackson
RCB, Executive Plaza South Rm 620
301/496-8611

RFP NCI-CP-33005-02
Title: Epidemiology survey of human retroviruses
Deadline: Approximately July 30

The Viral Epidemiology Section, Environmental Epidemiology Branch, Epidemiology and Biostatistics Program, NCI Div. of Cancer Etiology, is recompeting a project which is being performed by Research Triangle Institute. The objectives of this acquisition are: 1) to conduct surveys of the occurrence of human retroviruses in relationship to malignancy by collecting sera and other samples for serologic and virologic analysis from epidemiologically defined study populations, 2) to chart the distribution of HTLV-I in relationship to leukemia/lymphoma and other disease outcomes focusing in areas suspected to be HTLV-I endemic, 3) to explore the role of HIV as a cofactor for virally-associated cancer, and 4) to search for new human retroviruses suspected on the basis of epidemiologic or serologic evidence.

Project sites will be targeted by the NCI and the Principal Investigator based on the potential for exploring or settling specific questions. Choice of study sites will be based on new data contacts with local scientists with access to study populations and through results of ongoing studies in a specific locale with new initiatives growing out of results of unexpected findings. Under this proposed acquisition the Contractor shall be responsible for: a) consultations and collaborations with NCI Project Officer(s), other investigators designated by the P.O. and officials of international health organizations as directed by the P.O., b) surveys of existing and new sera, c) data and specimen collections based on epidemiologic protocols developed by the P.O. with appropriate approvals by properly constituted institutional review boards, d) assistance in forms and questionnaire design, e) quality control, standardization, and delivery of data tapes and samples, f) laboratory processing according to NCI procedures to be performed on site by the Principal Investigator and colleagues.

It is anticipated that a single award will be made for a period of five years with the anticipated award scheduled for Feb. 1, 1993. There are no limitations on the geographic location of the contractor. In order to be considered, the Contractor must meet three sets of requirements and specifications with regards to institutional (corporate) requirements, institutional experience and personnel requirements. These will be detailed in the solicitation package. A primary restriction will be non-interchangeability of the key personnel (substitutions of key personnel after award or resignation of key personnel may be cause for termination and recompetition of the contract).
Contract specialist: Michael Loewe
RCB Executive Plaza South Rm 620
301/496-8611

RFP NCI-CP-33002-21
Title: Retrovirus epidemiology and natural history in hemophiliacs and their sexual partners
Deadline: Approximately July 27

The Environmental Epidemiology Branch, Epidemiology and Biostatistics Program, NCI Div. of Cancer Etiology, is recompeting a current contract with Research Triangle Institute. NCI is seeking a contractor who will support the EEB by conducting epidemiologic and natural history studies of hemophiliacs (and persons with related disorders) and their sexual partners and family members, by the maintenance, acquisition and use of epidemiologic data bases, by providing support for collecting and handling biologic specimens and laboratory data, by statistical analysis of the data as directed by the Project Officer or his designee(s), and by responding quickly to request from the Project Officer involving certain priorities.

The contractor shall support four major projects: 1) follow-up of a cohort of hemophiliacs, 2) recruitment and follow-up of wives or steady female partners of hemophiliacs, 3) establishment and follow-up of a national and international registry for HIV-infected hemophiliac persons, and 4) other special epidemiologic studies. The types of activities needed to conduct these studies are divided into eight tasks which will be described in detail in the solicitation package. It is anticipated that an incrementally funded, cost-reimbursement, completion type contract will be awarded for a five-year period of performance.
Contract specialist: Barbara Shadrick
RCB Executive Plaza South Rm 620
301/496-8611

RFP NCI-CP-15621-21
Title: Tracing individuals for environmental epidemiologic studies of cancer (master agreement, annual resolicitation)
Deadline: Approximately Aug. 10

NCI's Div. of Cancer Etiology, Epidemiology & Biostatistics Program, Environmental Epidemiology Branch, is seeking to expand the existing Tracing Master Agreement pool with experienced firms to carry out tracing of epidemiologic study subjects. All MA holders already in the existing ma pool need not respond to this announcement. The MA pool currently consists of four organizations whose Master Agreements expire on June 27, 1995: Johns Holding Company (N01-CP-15621), Equifax Government and Special Systems (N01-CP-15707), Survey Research Associates, Inc. (N01-15708) and TRACERS Company of America, Inc. (N01-CP-15709). This acquisition is being advertised under a single umbrella title, A MA will be awarded under this title to each acceptable offeror, specifying the tracing method(s) in which the offeror has capability and experience as judged by the NCI. The three distinct categories of tracing methods to be used are listed below. Offerors may apply for any or all of these tracing methods, which are referred to as: M-1 -- Tracing Individuals Through Credit Bureaus, M-2 -- Tracing Individuals Through Motor Vehicle Bureaus, and M-5 -- Tracing Individuals Utilizing Other Resources and Sources.

Under this mechanism, experienced tracing firms are awarded a MA that authorizes them to bid on Master Agreement Order (MAO) RFPs which specify tracing tasks involving location of subjects who are designated as "difficult-to-find." This means that the subjects were not located during a variety of standard initial tracing procedures undertaken previously by NCI or other contractors. The subjects being traced for the purpose of vital status determination are included in research studies on cancer in relation to suspect environmental agents involving past exposure to chemicals in various forms and exposure situations, drugs, food components, radiation and biological agents such as viruses. Cancer patients, close relatives, comparison or "control" subjects, and individuals in high-risk families may also be sought. Last known vital status of subjects and associated dates may vary from recent years to 50 years ago. Levels of tracing difficulty will vary in accordance with the time-frame of the study, and on sex, age, marital status, and amount of known personal and demographic information available on the subjects. The time-frame is the range of dates of last known vital status on the records from which the cohort names were drawn, such as 1940-1953. In order to avoid study bias that may result from incomplete vital status determination, it is crucial to locate a maximum number of study subjects (at least 90 percent in cohort studies) within a relatively short time. In preliminary tracing

activities, NCI and/or contractors have already searched via basic tracing resources such as Social Security Administration, National Death Index, Health Care Finance Administration, state mortality files, Post Office address correction requests, etc., which (combined) yield the vital status of about 65% to 85% of the subjects in the cohorts being followed. The remainder, labelled "difficult-to-find", are the subjects to be sought through this MA/MAO RFP mechanism which involves three distinct tracing methods.

MAO RFPs will be sent only to MA Holders within the tracing pool, and MAO awards will follow after evaluation of the competing proposals. A separate Technical Proposal must be submitted when applying for this Master Agreement and each of the three tracing methods. Although a separate Technical Proposal will be required, only one Business Proposal is needed. Thus a firm experienced in all three tracing methods may submit four different Technical Proposals -- one for the Master Agreement and one for each of the three methods of tracing, if applicable. The Master Agreements will cover from the date of award through June 27, 1995. Master Agreements will be awarded to all firms whose Technical Proposals are considered acceptable. Multiple MAO/RFPs will be issued each year.

Contract specialist: Barbara Shadrick
RCB Executive Plaza South Rm 620
301/496-8611

RFA Available: CCOPs

RFA CA-92-15

Title: **Community Clinical Oncology Program**

Letter of Intent Receipt Date: June 29

Application Receipt Date: August 24

NCI's Div. of Cancer Prevention and Control invites applications for cooperative agreements to the Community Clinical Oncology Program. New community and research-base applicants and currently funded programs are invited to respond to this RFA.

This issuance of the CCOP RFA seeks to build on the strength and demonstrated success of the CCOP over the past nine years by continuing the program as a vehicle for supporting community participation in cancer treatment and cancer prevention and control clinical trials through research bases (clinical cooperative groups and cancer centers supported by NCI) and utilizing the CCOP network for conducting NCI-assisted cancer prevention and control research.

New applicants and currently funded programs are eligible as described below. Two categories of awards will be made: community programs and research bases. A community applicant may be a hospital, a clinic, a group of practicing physicians, a health maintenance organization (HMO), or a consortium of these. Community programs will be required to enter patients onto NCI-approved treatment and cancer prevention and control clinical trials through the research base(s) with which each CCOP is affiliated.

Research-base applicants must be either an NCI-funded clinical trials cooperative group or a cancer center. Research bases will be required to provide clinical research treatment and cancer prevention and control protocols, monitor the quality of the research, and follow CCOP accrual.

Support of this program will be through the cooperative agreement (U01). The total project period may not exceed three years for new applicants and five years for applicants currently supported under this program. Currently supported applicants will be funded for three, four, or five years depending upon priority score/percentile, review committee recommendations, and programmatic considerations.

It is anticipated that up to $2.5 million in total costs per year for five years will be committed to specifically fund applications submitted in response to this RFA. Of the total, approximately $300,000 will be committed to research bases and approximately $2.2 million to CCOPs. It is anticipated that up to 3 research base awards and up to 16 CCOP awards will be made.

Over 80 percent of patients with cancer are treated in the community. The CCOP was initiated in 1983 to bring the benefits of clinical research to cancer patients in their own communities by providing support for physicians to enter patients onto treatment research protocols. The second RFA, issued in 1986, expanded the focus to include cancer prevention and control research. In 1991, there were 52 programs in 27 states involving more than 300 hospitals and 2,600 physicians. Approximately 5,000 patients were entered onto treatment trials and 4,000 subjects per year onto cancer prevention and control studies.

Cancer prevention and control research in the CCOPs is aimed at reducing cancer incidence, morbidity, and mortality through the identification, testing, and evaluation of interventions in controlled clinical trials. The 80 protocols activated to date cover the full spectrum of cancer prevention and control research, including chemoprevention and marker studies for future prevention interventions, smoking cessation studies, screening and early detection, and pain control and other symptom management interventions.

The CCOP initiative is designed to bring the advantages of state-of-the-art treatment and cancer prevention and control research to individuals in their own communities by having practicing physicians and their patients/subjects participate in NCI-approved treatment and cancer prevention and control clinical trials. The CCOP also provides a mechanism to increase the involvement of primary health care providers and other health care specialists in treatment and cancer prevention and control research and provides an opportunity for education and exchange of information on new technologies.

For projects involving clinical research, NIH requires applicants to give special attention to the inclusion of women and minorities in study populations. If women or minorities are not included, a specific justification for this exclusion must be provided. Applications without such documentation will not be accepted.

Review criteria for CCOP applicants include the ability to accrue a minimum of 50 credits per year to cancer prevention and control clinical trials and at least 50 credits to cancer treatment clinical
trials. Review criteria for Research Bases include the ability to design appropriate treatment and/or prevention and control clinical trials. For both CCOPs and Research Bases the qualifications and experience of personnel and the stability and past performances of the functional unit applying will also be considered. The review group will examine submitted budgets and recommend an appropriate budget and period of support.

The anticipated date of award is June 1, 1993. NCI program staff will take into account demographic and geographic distribution of applicants in the final funding selection process to ensure inclusion of minority and underserved populations. If more than one CCOP applicant competes for the same patient population, all may not be awarded unless warranted by the population density.

Prospective applicants are asked to submit by June 29, 1992, a letter of intent that includes a descriptive title of the proposed research, the name, address, and telephone number of the Principal Investigator, the identities of other key personnel and participating institutions, and the number and title of the RFA in response to which the application is being submitted.

Letters of intent are to be sent to: Dr. Leslie Ford, Chief, Community Oncology and Rehabilitation Branch, NCI Executive Plaza North, Rm 300-D, Bethesda, MD 20892, phone 301/496-8541. Requests for the complete RFA and inquiries also should be directed to Dr. Ford.