THE CANCER LETTER

Vol. 17 No. 24
June 14, 1991

Price $205 Per Year US, Canada.
$230 Per Year Elsewhere

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

Bristol-Myers, USDA Agreement On Yew Harvest Is Near; Agencies Plan Public Briefings On Taxol

Bristol-Myers Squibb Co., the U.S. Dept. of Agriculture and the Bureau of Land Management are close to finalizing an agreement that would allow the harvesting of Pacific yew trees on federal lands controlled by USDA, NCI sources said this week. The bark of the yew is at present the only source of the promising anticancer drug taxol. NCI, Bristol-

(Continued to page 2)

In Brief

Ling, Vogt, Hartwell Win General Motors Prizes; Fox Chase Hires Four Scientists; Vitetta Honored

THREE SCIENTISTS are recipients of the 13th annual General Motors Cancer Research Foundation prizes, which total $390,000. The winners are **Victor Ling,** Univ. of Toronto/Ontario Cancer Institute, and member of NCI's Div. of Cancer Treatment Board of Scientific Counselors, who received the Charles Kettering Prize for his discovery of a protein that pumps drugs out of malignant cells; **Peter Vogt,** Univ. of Southern California School of Medicine, winner of the Charles Mott Prize for discovery of the cancer causing gene called jun; and **Leland Hartwell,** Univ. of Washington (Seattle), who was awarded the Alfred Sloan Prize for his discovery of "inspector" genes that protect a cell from defects. Each receives a $100,000 award and $30,000 for a scientific workshop. . . . **FOX CHASE** Cancer Center recently hired four scientists: joining the medical science division is **Gary Kruh,** senior staff fellow in the NCI Div. of Cancer Etiology Laboratory of Cellular & Molecular Biology, and **Anil Jaiswal,** assistant professor of cell biology at New York Univ. Medical Center; **Heinrich Roder,** Univ. of Pennsylvania School of Medicine, will direct the center's nuclear magnetic resonance facility, and **Eileen Jaffe,** who was associate professor of biochemistry at Univ. of Pennsylvania School of Dental Medicine, will study enzyme reactions. . . . **ELLEN VITETTA,** director of Univ. of Texas Southwestern Medical Center's Cancer Immunobiology Center, has received the 1991 Excellence in Science Award from the Federation of American Societies for Experimental Biology. . . . **UNIV. OF TEXAS** Board of Regents has established a $1 million endowment for bone marrow transplantation programs at M.D. Anderson Cancer Center. The John S. Dunn Sr. Endowment for the International Bone Marrow Transplantation Center was created with a $500,000 pledge from the John S. Dunn Research Foundation an $500,000 from institutional and private philanthropic funds. . . . **ISRAEL CANCER** Research Fund recently awarded research grants totaling $2.1 million to 89 Israeli scientists.

Agreement On Yew Harvesting Near; NCI, USDA Plan Taxol Briefings

(Continued from page 1)

Myers and USDA have tentatively scheduled briefings on June 18-19 for federal agencies, interest groups, and the media to discuss the agreement.

While provisions of the agreement were not available by presstime this week, **The Cancer Letter** has learned that in return for harvesting of yew on federal lands, Bristol-Myers has proposed to pay for a nationwide inventory of yew trees in the national forests. USDA would provide Bristol-Myers with samples of bark and needles from various forests for analysis of taxol content, with the hope of finding a renewable resource.

The agreement was undergoing final review this week, and its signing was "imminent," NCI executives said this week.

Bristol-Myers, which has a Collaborative Research & Development Agreement (CRADA) with NCI for taxol development, hopes to procure 750,000 pounds of yew bark this year. Harvesting is "on schedule," and as of early May, the firm had collected about 25 percent of that amount, NCI Div. of Cancer Treatment Director Bruce Chabner told the National Cancer Advisory Board at its May meeting.

This amount of bark will provide "a sufficient supply of taxol to provide for experimental use and some compassionate use," Chabner said. NCI hopes to open taxol to compassionate use next month.

In the CRADA, Bristol-Myers agreed to provide one kilogram of taxol for compassionate use this year. Taxol will be supplied directly to the cancer centers, where the decisions on patient eligibility will be made, Chabner said.

THE CANCER LETTER

Editor: **Kirsten Boyd Goldberg**
Associate Editor: **Lisa M. O'Rourke**
Contributing Editor: Jerry D. Boyd

Editorial/Subscriptions Office
PO Box 15189, Washington, DC 20003
Tel: (202) 543-7665 Fax: (202) 543-6879

Subscription rate $205 per year North America, $230 elsewhere. ISSN 0096-3917. Published 48 times a year by The Cancer Letter Inc., also publisher of The Clinical Cancer Letter and AIDS Update.

Treatment Referral Center

Because of the immense interest in taxol as a treatment for ovarian cancer--with about 10,000 to 12,000 potential candidates for the treatment this year--NCI has been "besieged" by requests to consider patients for treatment, Chabner said. NCI has responded by setting up a treatment referral center run by the Cancer Therapy Evaluation Program. The center provides information by telephone on taxol trials and other alternatives for treatment of ovarian cancer.

The center also provides patients and physicians with information on commercially available drugs, such as the recently approved hexamethylmelamine, and other combinations determined to be active in patients who have failed platinum, Chabner said. The service also will provide referrals to clinical or comprehensive cancer center protocols.

"We had a meeting with the cancer centers in which we outlined the proposal, and they willingly accepted responsibility for dealing with referrals and setting up protocols and facilities to handle inquires," Chabner told the NCAB.

The major problem with taxol has been getting enough of the drug. Complicating matters is the environmental issue: the only way to obtain the drug is by cutting down the yew trees and harvesting the bark, and this has been done primarily through clearcutting.

"Harvesting of the yew tree is caught in a larger question, the use of the ancient forests in the Northwest," Chabner said. "Environmental opposition to clearcutting, which is the most efficient way of harvesting lumber and yew, stems from the desire not to destroy the natural habitat of a number of species, including the spotted owl, and to prevent the erosion of the land.

"The vocal opposition to yew tree harvesting has coalesced in Oregon. There are environmental organizations now that are specifically protesting the harvesting of yew, and making all sorts of accusations of 'a veil of secrecy' surrounding the whole business of taxol harvesting and development," Chabner continued. "As you know, we try to make this a very public operation. We've appeared before this board and the Board of Scientific Counselors to explain each step in the development. Nevertheless the environmentalists are not satisfied that we are not making efforts outside of the harvesting of yew tree, and are attempting to block the harvesting of the yew forest."

The public briefings scheduled for next were planned partly in order to combat the secrecy charge.

Two lawsuits are being heard in federal courts in the Northwest to block clearcut harvesting in the national forest, Chabner said. One suit would set aside millions of acres of land as habitat for endangered species, while the other would block clearcutting, he said. "It's a very tangled and politically sensitive issue."

Despite the accusations of environmentalists, NCI is making efforts to develop taxol from renewable sources. NCI executives recognize that, "As long as we have to obtain it from trees, the supply of taxol will be precarious and probably inadequate," Chabner said.

NCI expects to fund nine or 10, and possibly more, of the 61 grant applications submitted in response to an RFA issued late last year on methods of taxol synthesis. NCI executives may nominate some of the applications for the new NIH Shannon Awards mechanism for grants that fall just below the payline.

NCI is also exploring plant hedging, or using clippings from common commercial varieties of yew, to obtain drug. Univ. of Mississippi has undertaken extensive evaluation of the taxol content of commercial yew trees and has evidence that this may a commercial source, Chabner said. "We feel this may, in a reasonable period of time, become an alternative source for taxol," he said.

In addition, "There is extensive search for taxol from needles of other trees besides the Pacific yew. There are stands of trees in Canada, the Himalayas, and the Soviet Union which are being examined. We have a number of collaborators who are taking part in this," Chabner said. The supply of the yew itself is not endangered, he emphasized.

"This is one of the most interesting issues, mixing science, clinical trials, and the politics of the environment, and I hope it will have a happy outcome," Chabner concluded in his talk to the Board.

NCI Director Samuel Broder said the Institute must "respect and honor" the environmental issue. "In the long run, we will have renewable resources or synthetic resources, which will make the issue of taxol exclusively from the bark of the yew tree a historical episode," he told the Board. "Nonetheless, we do have to deal with the short term. There are 12,500 women a year who die of ovarian cancer, and we feel that we need to make sure that those women who are eligible and perhaps likely to benefit from this drug have access to it."

Broder's comment is a brief summary of NCI's position regarding the short term need for bark for taxol. While Bristol and USDA were working on their agreement on harvesting yew of USDA lands, the Dept. of the Interior had issued proposed rules for protection of the habitat of the Northern spotted owl. The rules, published in the May 8 "Federal Register," would set aside 11.6 million acres of federal, state, and private land for "Habitat Conservation Areas" that would be preserved to support the owl, which was determined to be a threatened species.

NCI responded to the proposed rules in a letter to Interior pointing out the emergency need for taxol and asking that the yew harvest be allowed to continue in the conservation areas, according to NCI sources. The Interior Dept. had scheduled public hearings on the rules in California, Washington, and Oregon, and plans to issue revised rules following the hearings.

In clinical trials, taxol activity is being tested and confirmed, not only in ovarian cancer, but breast, lung, gastrointestinal, and other tumors. NCI is planning trials to test taxol in combination with other cytotoxic drugs.

A phase 2 trial is currently underway in platinum resistant ovarian cancer, testing the maximum tolerated dose of 250 mg/m^2 continuous infusion for 24 hours accompanied by G-CSF rescue. About 14 patients have been entered, Chabner said.

Though it is too early to discuss therapeutic results of the phase 2 trial, Chabner said, the phase 1 study, which had about a 33 percent response rate, "confirmed that we can use the drug in higher doses with G-CSF and with a promising response rate."

In breast cancer, a small phase 2 trial at M.D. Anderson Cancer Center resulted in complete and partial responses exceeding 50 percent, the first phase 2 study reported for taxol in breast cancer. The report on the study was not accepted for presentation at the American Society of Clinical Oncology scientific sessions this year, but the study's abstract was published in the meeting proceedings.

Frankie Holmes of M.D. Anderson's Medical Breast Cancer Section was study chairman. She reported that 25 patients with metastatic breast cancer and who had received prior chemotherapy were given taxol by 24 hour infusion every three weeks. The starting dose was 250 mg/m^2 (200 mg/m^2 in seven patients who had had irradiation to marrow or poor marrow tolerance to prior chemotherapy). To prevent allergic reactions, all patients received decadron, cimetidine, and diphenhydramine.

Objective remissions reported in the abstract totaled 48 percent, with 12 percent complete remissions. An update placed total response at more than 50 percent.

Hematologic toxicity was dose limiting in all but one patient, in whom myalgias necessitated dose

reduction. Neutropenia with fever requiring intravenous antibiotics occurred in 36 percent of patients, which Holmes said was surprisingly few considering given the low granulocyte nadir. Alopecia was total in all of the patients, and other toxicities were mild except an apparently peak-dose sensitive myalgia-arthralgia, grade 2 (68%), grade 3 (8%).

The investigators concluded that taxol is very active for metastatic breast cancer and called for tests with taxol in combination with other agents and growth factors to modulate myelosuppression. The combinations should be tried in previously untreated patients, they suggested.

M.D. Anderson, in fact, is starting another phase 2 trial, using taxol with adriamycin and G-CSF for treatment of previously untreated patients with metastatic breast cancer.

NCI's Medicine Branch has begun a trial which opened in April combining taxol and adriamycin. "We believe these are the two most active drugs, although the data for taxol is quite limited, but we feel it is important to explore the combined uses of these drugs," Chabner said. "The overlapping toxicity consists of marrow suppression. This potentially could be dealt with by using G-CSF."

In addition, CTEP has a number of ongoing phase 2 trials, in gastrointestinal cancer, lung cancer, and most of the solid tumors. The Gynecologic Oncology Group is conducting a study of taxol plus cisplatin versus cytoxan plus cisplatin, the standard therapy in advanced ovarian cancer, as primary treatment for ovarian cancer.

Group Chairmen Advise Seven Trials For Series 4 High Priority Program

Seven phase 3 clinical trials being carried out by the clinical cooperative groups were recommended for the NCI High Priority Trials program by group chairmen at their meeting in Bethesda last week. The Div. of Cancer Treatment Board of Scientific Counselors gave the trials final approval this week.

The trials will be the fourth series in the program which started in 1988. They will replace eight from the first three series which will be closed by the end of 1991.

High priority designation qualifies a trial for per capita reimbursement to those groups entering patients in it. NCI considers the program in general to be highly successful in speeding accrual. In series 1 and 2, high priority trials accrued 27 percent of phase 3 patients although they represented only six percent of active phase 3 studies.

The chairmen selected the new candidate trials by voting on a list of nine suggested by DCT's Cancer Therapy Evaluation Program. Richard Ungerleider, chief of the Clinical Investigations Branch, suggested that only six trials be selected although eight are being closed. The chairmen each voted on six, but seven wound up with seven to 10 votes. CTEP Director Michael Friedman said he would present all seven to the DCT board. They are:

▶National Surgical Adjuvant Breast & Bowel Project trial to evaluate the worth of tamoxifen in conjunction with lumpectomy and breast irradiation for the treatment of noninvasive intraductal carcinoma of the breast (10 votes from the chairmen).

▶An intergroup study (Eastern Cooperative Oncology Group and Radiation Therapy Oncology Group) of postoperative adjuvant therapy in patients with completely resected stage 2 and stage 3A nonsmall cell lung cancer. Patients are randomized to thoracic radiotherapy alone or to thoracic radiotherapy plus cisplatin and VP-16 (eight votes).

▶Intergroup trial of adjuvant chemoradiation after gastric resection for adenocarcinoma. Patients are randomized to observation or to 5-FU plus leucovorin followed by radiation plus 5-FU plus leucovorin followed by two more cycles of 5-FU plus leucovorin (eight votes).

▶Cancer & Leukemia Group B study of high dose cyclophosphamide/cisplatin/BCNU as consolidation to adjuvant CAF for patients with operable stage 2 or stage 3 breast cancer involving 10 or more axillary lymph nodes. The Southwest Oncology Group also is interested in participating in this study (seven votes).

▶Intergroup (ECOG, SWOG, CALGB) study of conventional adjuvant chemotherapy vs. high dose chemotherapy and autologous bone marrow transplantation as adjuvant intensification therapy following conventional adjuvant chemotherapy in patients with stage 2 and 3 breast cancer at high risk of recurrence. Patients are randomized to CAF plus radiation therapy plus tamoxifen plus 5-FU, or to CAF followed by bone marrow harvest, high dose chemotherapy, autologous bone marrow transplant, GM-CSF, to be followed by radiation, tamoxifen, and 5-FU (seven votes).

▶Intergroup (ECOG, CALGB) post operative adjuvant interferon alpha 2 in resected high risk primary and regionally metastatic melanoma. Randomization will be to observation vs. high dose interferon for one year vs. low dose interferon for two years (seven votes).

▶ECOG and SWOG evaluation of hormonal therapy

vs. observation in patients with stage D_1 adenocarcinoma of the prostate following pelvic lymphadenectomy and radical prostatectomy. Patients will be randomized to hormonal therapy of either zoladex or orchiectomy vs. observation. Those progressing in the observation group will then receive hormonal therapy (seven votes).

Two trials on the list submitted by CTEP for consideration received only three votes each and were not be recommended to the DCT board. They are an intergroup study (with SWOG the only participant so far) of adjuvant intraperitoneal interferon in stage 3 ovarian cancer with no evidence of disease after surgery and chemotherapy; and a North Central Cancer Treatment Group study of megace in selected patients with malignant melanoma.

Robert Park, chairman of the Gynecologic Oncology Group, pointed out that GOG has an ongoing study similar to the intergroup ovarian cancer trial, using the agent P32, a radioactive phosphate. Eighty nine patients have been accrued since 1987, with a projected goal of 150. The intergroup study limits chemotherapy to platinum based regimens.

The NCCTG melanoma study received little support when it was pointed out that a previous melanoma study using megace had been stopped after 120 patients because of slow accrual. Followup showed a highly significant advantage in favor of megace. The present trial randomizes stage 1 and 2 patients after surgery to placebo or two years of megace.

AACR Considers Foreign Member Status, Meetings With ASCO

Members of the American Assn. for Cancer Research considered two potentially divisive issues at their annual meeting last month in Houston: The membership status of foreign scientists, and AACR's relationship with the American Society of Clinical Oncology.

President Harold Moses, immediately upon taking over from Bernard Weinstein, asked for discussion on both issues. The first was a proposal to allow non-U.S. scientists full membership. They are now carried as "corresponding" members, and account for about 20 percent of AACR's membership. They cannot vote or hold offices in the association.

Although Moses clearly stated at the start of the discussion that a name change was not being considered (retaining American), several members argued indignantly that they opposed changing the name to reflect a new, international status.

Another member said, "I find the whole idea bizarre. Does that mean we could have a foreign president? What would it do to our effort to lobby Congress?"

Another noted that AACR and the U.S. cancer research effort depended on the "largess of the American people, as taxpayers and supporters of charitable organizations."

One member commented, however, that "I'm just as chauvinistic as the next guy, but that has nothing to do with the structure of this organization. Cancer is a worldwide problem. Cancer research should be promoted internationally, as broadly as possible."

As for foreigners holding office in AACR, several responded to the effect, "So what?"

A motion by John Weisburger to eliminate the corresponding and have only one category of membership was withdrawn when Moses pointed out that it involved a bylaws change. Those changes have to first be considered by the Bylaws Committee and presented to the membership for vote by mail.

The other issue, whether to continue meeting in tandem with ASCO, may be more difficult to resolve. James Holland, an active and vocal member of both organizations, said that "eight days away for those of us who are vitally interested in the activities of both AACR and ASCO is a high price to pay."

Holland suggested that each organization have its own, separate meeting of two to three days, at different times of the year. Members of either would be permitted to attend both.

Former AACR President Lawrence Loeb, harking back to the first issue, said that "we may have more in common with scientists around the world than with physicians who treat cancer."

"I invite Dr. Loeb to reconsider that remark," Holland said. "There might be some of us here who are interested in something more than pushing pills."

Loeb did reconsider. "There is nothing more important to our society than having as members physicians who understand science."

Moses pointed out that ASCO's size (approaching 9,000 members) limits the annual meetings to those cities with convention facilities large enough to handle it. AACR would be more flexible in where it could have its meetings, he inferred.

Moses said that AACR is locked into meeting sites with ASCO through 1994, although tentative sites have been selected into the next century.

An ad hoc committee chaired by Sharon Murphy will study both issues.

Holland brought up the subject later that week, at ASCO's business meeting, commenting that, "This is now my eighth day in Houston, and it is taxing to be

away from home base for so long. The concept of AACR and ASCO meeting back to back may have outlived its usefulness." He noted that "AACR is considering separating from ASCO," and suggested that ASCO also discuss the issue.

"Thank you for your comment," ASCO President Harvey Golomb responded, moving on to the next new business item.

Evaluation Finds OIGs Effective In Providing Flexibility To PIs

A pilot evaluation of NCI's Outstanding Investigator Grants mechanism has found that the seven-year awards generally have had the intended effect of providing principal investigators with the flexibility to engage in innovative or high risk research, or pursue new research opportunities.

NCI began the OIG in 1985 to provide long term support to scientists with outstanding records in cancer research to pursue projects of unusual importance to the National Cancer Program.

The evaluation of the OIG was conducted to answer several questions about whether the grants mechanism was having the intended effect.

Sources of data for the preliminary analysis were the written responses provided by the first cohort of type 2 OIG applicants and by reviewers of those applications to two sets of evaluation questions. Bibliographies submitted by the applicants also were used for a preliminary analysis of scientific output.

"It was felt that this was a first attempt at trying to obtain such information, and the information received could be indicative of what might be requested further in the evaluation of this mechanism," said Bernard Fisher, chairman of the Planning and Budget Committee of the National Cancer Advisory Board, which discussed the preliminary study at its May meeting.

According to the study's summary, preliminary evidence was presented to demonstrate that:

--The OIG offered the PIs the flexibility to engage in self-described innovative or high risk research endeavors and allowed them to pursue new research opportunities.

--The majority of the research supported was cancer related and several investigators pursued more cancer relevant research after the award was made.

--The mechanism did relieve the grant related administrative burden associated with managing the research program.

--The OIG has had no detectable effect (either positive or negative) on the scientific output of this cohort of investigators: their scientific output remained high.

The preliminary study recommended that a full scale evaluation not be conducted until a larger number of OIGs have been awarded and in place long enough for citation data to accumulate for those research publications generated with OIG funding.

OSI Investigated 104 Misconduct Allegations, Finds Misconduct 'Rare'

The NIH Office of Scientific Integrity has resolved 104 allegations of scientific misconduct in the past two years, and has an active case file of about 60 to 80 cases, an OSI official told the National Cancer Advisory Board recently.

In about 20 to 25 of the resolved cases misconduct was found, though most have been "remedial in nature," said Clyde Watkins, acting deputy director for OSI. "We can say that scientific misconduct is rare."

Allegations are received by the office usually from the institution or from phone calls, usually from persons who wish to remain anonymous, Watkins said. The office is authorized to act on anonymous complaints, which allows whistleblowers to come forward, he said.

"We take the allegation away from the complainant, so that it's no longer complainant versus respondent," Watkins said. The office, staffed entirely by scientists, conducts an initial review to determine the basis of the complaint.

About 70 percent of complaints go on to become full inquiries. "Quite a large number of allegations don't make it. Either they don't fit in the Public Health Service view of misconduct, or there was an honest error or difference of opinion," Watkins said. "Unfortunately, this information is seldom released to the public."

Some complaints are the result of sloppy scientific work, and as such are not misconduct. "OSI doesn't try to fit everything under the sun into scientific misconduct, though we have been accused of doing so," Watkins said.

Allegations made in bad faith are actionable, and one such case is currently being investigated, Watkins said.

Watkins addressed the fact that, "whenever there is an investigation, an individual's reputation is damaged." It is rare that the investigation is kept entirely confidential, though he stressed that leaks to the press and others "do not come from OSI."

When an investigation has cleared a scientist, the case records are kept confidential, and while some

scientists want an announcement that they have been cleared made, "most want it to be dropped," Watkins said.

Two suits have been filed against OSI alleging violations of the Administrative Procedures Act.

NCAB member John Durant said he was concerned that there is no statute of limitations on misconduct investigations. "We wish there was," Watkins said, noting that one case goes back to 1972.

On Durant's initiative, the NCAB passed a resolution recommending that NCI staff encourage HHS to adopt a statute of limitations of seven years for investigations conducted by OSI. Violations of the human rights of subjects would be excluded from the limitation.

The NCAB also encouraged the OSI to make public data on the outcome of investigations to make clear how many total investigations have been done and the number of investigations that resulted in action, and those that were cleared.

OSI's budget is about $1.6 million annually.

Medically Disadvantaged Targeted In PA Approved By DCPC Advisors

NCI's Div. of Cancer Prevention & Control Board of Scientific Counselors has given concept approval to a program announcement on model cancer control delivery systems for the medically disadvantaged.

Following is the concept statement:

Model cancer control delivery systems for the medically disadvantaged. Concept for a new program announcement.

The goal of this project is to develop, implement and evaluate organizational models for making cancer prevention and control services more accessible to poor, minority, and medically disadvantaged populations. These populations, which suffer a disproportionate share of the burden from cancer, frequently utilize services delivered through community and migrant health centers, public health clinics and public and university hospitals. However, public or community health clinics generally do not offer cancer prevention and control services as part of the routine delivery of health care.

Accomplishment of this research will require a multidisciplinary research team comprised of health service delivery providers and public health and medical research scientists with experience in cancer prevention and control.

To date, NCI has funded projects in 29 state health departments to build their capacity to plan and implement cancer control programs. These awards have helped states to develop state cancer plans, train public health personnel in cancer prevention and control, establish surveillance systems, and acquire experience in initiating and evaluating specific cancer prevention and early detection interventions. The next step is to develop, implement and evaluate organizational models for making cancer prevention and control services more accessible to the medically underserved populations that use public health care delivery systems.

The major research question to be answered is whether cancer prevention and early detection services can be successfully integrated with other preventive or medical services being offered to populations not likely to receive cancer services otherwise. The primary objectives of this research are:

1. To test the feasibility and effectiveness of modifying existing community and public health care delivery systems, such as community health centers, public health clinics, and hospital outpatient clinics, to increase delivery and utilization of counseling and early cancer detection screening regimens.

2. To test the effectiveness of these interventions in improving knowledge, attitudes and practices of public health clientele with respect to cancer prevention and control.

Applicants will be required to assess what changes to the health care system are necessary in order to integrate cancer prevention and control services into usual care, develop strategies to implement these changes and evaluate their impact on knowledge, attitudes, and practices of public health clientele. In developing strategies, special consideration should be given as to how the cancer prevention and control services can build upon existing medical or health promotion services and the interest and expertise of existing personnel.

The "delivery system" should be defined in terms of resources and organization. Interventions should be evaluated in terms of their effectiveness in improving knowledge, attitudes and practices of public health clientele with respect to cancer prevention and control.

Strong experimental or quasi-experimental designs must be proposed to evaluate interventions. For example, multiple clinic/health center sites could be randomized to compare changes in measures of cancer prevention between intervention and comparable control sites. Regardless of the design, evaluation must occur at the levels of both the clinic and the individual. Organizational strategies that may improve utilization of preventive services may include, but should not be limited to, use of computer reminder systems, medical record prompts, checklists, or use of allied health personnel to deliver preventive procedures. However, interventions tested must include strategies to encourage the patient to return to the index facility, or a more appropriate facility, for follow up or periodic rescreening as necessary. Investigators must track the initial prevalence screen, as well as ongoing subsequent screens.

Investigators will be required to document access to high risk groups (low socioeconomic status, uninsured or minority populations) through the health care systems under study. Plans to implement procedures that assure compliance with appropriate followup recommendations, should they be needed, must be explicitly described. This must include a detailed plan on how treatment will be arranged and who will pay for it. All clinical, laboratory, or other medical procedures performed in relation to the grant supported interventions must meet state of the art levels. Validation that tests or procedures have been received is required (e.g., through medical records), and information regarding costs associated with interventions and procedures also must be compiled.

Potential applicants are official health service delivery organizations or institutions, such as health departments, community health centers, or hospitals providing care to the target populations, in collaboration with public health and medical research scientists experienced in cancer prevention and control. Given the reality that health service agencies rarely have the expertise or resources to conduct research and rigorously evaluate health promotion/disease prevention programs, significant collaboration with experienced investigators at cancer centers or universities is required. It is preferable that the health service agency be the lead applicant. If this is not possible, the lead

organization must demonstrate that the service agency has been integrally involved in the development and design of the project. Applications also will be accepted from consortia or national organizations of health agencies. However, as is the case for all applicants, a specific research design and intervention sites must be identified in the proposal. The multidisciplinary research team should demonstrate expertise in cancer prevention and control intervention and applications research and in the delivery of clinical services to high risk populations. A proven track record of collaboration among the proposed team is highly desireable.

Primary consideration in the review will be given to the innovativeness of the intervention and its appropriateness to and potential impact on the target population. Applicants must demonstrate how their interventions are new or different from previous research projects funded by NCI or others. Pretested materials should be used where possible.

RFA Available

RFA CA-91-16

Title: New Therapeutic Approaches to the Treatment of Prostate Cancer

Letter of Intent Receipt Date: July 22

Application Receipt Date: October 15

NCI's Div. of Cancer Treatment invites research grant applications (R01) from interested investigators to perform clinical studies in prostate cancer to improve treatment results and clinical outcome. Investigators are encouraged to utilize laboratory advances in understanding tumor growth and hormonal control in prostate cancer to develop an integrated research program of laboratory experimentation and concurrent clinical studies. New and experienced investigators in relevant fields and disciplines may apply to fund therapeutic clinical studies.

The incidence of prostate cancer continues to increase each year and has now surpassed lung cancer to become the most common carcinoma in males. It is estimated that approximately 122,000 new cases will be diagnosed in 1991 accounting for 19 percent of all male cancers. Black men in the U.S. have the highest rate of prostate cancer in the world. At the time of presentation, more than 50 percent of newly diagnosed patients will have either locally advanced of metastatic disease. Prostate cancer is the second leading cause of death from neoplasia among men, with more than 32,000 deaths estimated for 1990. It is an important cause of morbidity and mortality in the elderly. These upward trends are expected to continue as the male population ages.

When prostate cancer is diagnosed early while still confined to the prostate, the disease is curable with radical prostatectomy or radiation therapy. For patients with more advanced stages, initial treatment is based on prostatic cancer cell growth's presumed hormonal dependence and includes surgical castration and diethylstilbestrol. In recent years, new methods of hormone treatment utilize pharmacologic agents capable of reducing or blocking the action of testosterone, the major circulating androgenic hormone, by interrupting the complex interactions between the hypothalamus, pituitary, testis, and adrenal glands. However, these new therapeutic agents do not prevent the emergence of hormone-resistant cells. Advanced prostate cancers ultimately fail to respond to androgen deprivation. The mechanisms involved in the development of androgen resistance are not understood. There is no alternative therapy that can be offered at present to these patients that consistently results in reduction in tumor mass or palliation of symptoms.

In recent years, basic researchers have made promising new advances in understanding the mechanisms of growth control in the human prostate cell. The growth and differentiation of benign and malignant prostatic epithelial cells are regulated by androgens which in turn are modulated by growth factors and other hormones.

Clinical trials utilizing suramin, which interferes with heparin-binding growth factors, have recently shown responses in advanced prostate cancer. The mechanism of action of suramin is still not completely understood and ancillary laboratory studies are needed. In addition, biological response modifiers in combination with chemotherapy have achieved promising results in other tumor models but have not been adequately explored in prostate cancer.

Recent advances in understanding the molecular and cellular mechanisms operative in resistance to chemotherapy have led to the design of new therapeutic strategies to overcome drug resistance in other tumors. Many opportunities exist to develop new treatment strategies in prostate cancer utilizing laboratory advances in understanding tumor growth and hormonal control.

The major goal of this RFA is to foster clinical trials for patients with prostate cancer. Investigators are encouraged to propose pilot therapeutic clinical studies or new clinical trials (Phase I, II, or III) designed to improve therapy in prostate cancer patients. The application may include ancillary laboratory studies linked to the clinical trial. Applications must be focused on integrating clinical goals with laboratory research areas.

This RFA envisions funding therapeutic clinical studies that test and exploit basic findings concerning cellular targets of treatment or response to drug or hormone therapies. Clinical studies should involve human subjects and be designed to improve cancer treatment.

Examples of clinical studies include:

(1) growth factor or hormone therapies utilizing new agents; (2) treatment therapies for overcoming hormone, drug, or radiation resistance; (3) treatment therapies based on novel mechanisms of action; (4) biologics in combination with drug or radiation regimens; (5) new therapies combining endocrine manipulations with chemotherapeutic agents; and (6) radiation modifiers to enhance cell kill or protect normal tissue.

Laboratory research studies that are relevant to the therapeutic clinical studies may be included. Investigators already participating in relevant ongoing clinical trials are encouraged to develop related complementary laboratory studies. Laboratory experimentation may be designed to examine mechanism of action, mechanism of resistance, or conduct pharmacological analysis of the antitumor agents utilized in the patient studies. Laboratory studies designed to improve diagnosis or studies examining benign prostate disease are not applicable.

Approximately $750,000 in total costs per year for three years will be committed specifically to fund applications submitted in response to this RFA. It is anticipated that three to four awards will be made.

The earliest feasible start date for the initial award will be July 1, 1992.

Nonprofit organizations and institutions, governments and their agencies, and occasionally individuals are eligible to apply. For profit organizations are also eligible unless specifically excluded by legislation. Both domestic and foreign applicants may apply. Applications may be submitted from a single institution or may include arrangements with multiple institutions (e.g., consortia and Clinical Trials Cooperative Group) where appropriate.

Copies of the complete RFA and additional information concerning the objectives and scope of this research may be obtained from:

Diane Bronzert, Cancer Therapy Evaluation Program, Div. of Cancer Treatment, NCI, Executive Plaza North, Room 734, Bethesda, MD 20892, phone 301/496-8866, FAX: 301/480-4663.