THE CANCER LETTER

Vol. 18 No. 45
Nov. 20, 1992


Price $215 Per Year US, Canada.
$240 Per Year Elsewhere

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

## Taxol Recommended For Second Line Therapy In Platinum-Resistant Metastatic Ovarian Cancer

Taxol, the novel anticancer agent derived from the bark of the Pacific yew tree, was recommended for approval this week by FDA's Oncologic Drugs Advisory Committee.

In a unanimous vote, the committee recommended taxol for treatment of metastatic ovarian cancer in patients "who have failed first line chemotherapy or subsequent chemotherapy," in a motion by committee member Paul Bunn, Univ. of Colorado.

The committee and FDA officials praised taxol sponsor Bristol-Myers

(Continued to page 2)

*In Brief*

## Hammond Resigns As ACS Officer; Wykoff Slated To Direct FDA Special Populations Office

**DENMAN HAMMOND** has resigned as an officer of the American Cancer Society because of demands on his time as president of the foundation supporting the Children's Cancer Study Group and in administering the group's operations office. Hammond's resignation as chairman of the group is effective this month, with **Archie Bleyer** of M.D. Anderson taking over. However, Hammond had to assume responsibilities of CCSG administrative officer when John Weiner left three months ago due to family illness. Hammond is recruiting a replacement. He will remain on the ACS Board of Directors, but his resignation as an officer, and as chairman of the Medical and Scientific Committee, takes him out of the succession to the ACS presidency. . . . **RANDOLPH WYKOFF**, director of FDA's Office of AIDS Coordination, will head FDA's proposed Office of Special Populations when the new office is approved by HHS (**The Cancer Letter**, Nov. 13). At first, the office will liaison with cancer, AIDS and Alzheimer's patients and their advocates, but will add other serious or life-threatening diseases as need requires, according to an FDA spokesman. The AIDS office will cease to exist as a separate entity. . . . **RAYMOND HOUDE**, senior attenting physician in the Pain Service of Memorial Sloan-Kettering Cancer Center, received the Bristol-Myers Squibb Award for Distinguished Achievement in Pain Research at the American Pain Society meeting in San Diego. . . **CHARLES SCHIFFER**, professor of medicine and oncology, Univ.of Maryland Cancer Center, is the new chairman of FDA's Oncologic Drugs Advisory Committee, succeeding Craig Henderson. New member **Albert Siu**, assistant professor of geriatric medicine, Univ. of California at Los Angeles, succeeds Grace Monaco as consumer advocate member of the committee. Siu is a board member of the National Coalition for Cancer Survivorship.

## Taxol Recommended As 2nd Line Rx In Platinum-Resistant Ovarian Cancer

(Continued from page 1)

Squibb Co. for its lucid presentation at the Nov. 16 meeting and in the New Drug Application submission, but the committee paid the highest compliment by ending the deliberations one hour earlier than scheduled.

Sources said the drug could be on the market as early as January barring unexpected delays. FDA still must work with the company to satisfy matters related to labeling, purity, and environmental impact of the drug's approval.

In its discussion, the committee primarily was concerned about the suggested dose of taxol. On a motion by Bunn, the committee recommended, in a 10-1 vote, a dose of 135 mg/m$^2$ 24 hour infusion pending the results of a large study in Europe and Canada which is testing two doses (135 mg/m$^2$ vs. 170 mg/m$^2$) and two administrations (24 hour vs. 3 hour) of taxol in ovarian cancer.

The one dissenting vote was cast by Harold Harvey, Univ. Hospital, Hershey, PA, who argued that the middle dose of those tested in phase 2 trials, 170 mg/m$^2$, which the company had recommended in the NDA, should be approved. "I can't think of any instance in oncology when you would choose the lower dose," he said.

Data from the five trials the company presented did not show a clear advantage for the higher dose, other committee members said.

In the absence of a distinct benefit, and when toxicities of the higher dose are greater, "you have to pick the safest dose that is efficacious," Bunn said.

The committee's dosage recommendation could become moot when data from the ongoing European-National Cancer Institute of Canada study are available next year, FDA oncology reviewer Grant Williams said.

Elizabeth Eisenhower, of NCI-Canada, said data are expected to be presented at the American Society of Clinical Oncology annual meeting next May in Orlando, FL.

### BMS Presentation

Renzo Canetta, Bristol vice president, presented data from five clinical trials of taxol in ovarian cancer, involving 192 patients, all but two of whom had prior platinum-containing chemotherapy.

The company also reviewed the literature over the past 10 years and identified 150 trials, of 58 compounds, in advanced ovarian cancer. Response rates did not exceed 20 percent in 16 trials of single agent cisplatin, carboplatin, or iproplatin, and most patients develop resistance. Response rates did not exceed 17 percent in trials of a number of other compounds including altretamine, thiotepa, ifosphamide, mitomycin, and etoposide.

Following is a summary of the data presented:

▶Johns Hopkins Oncology Center protocol 013. Accrual began in July 1986, 46 patients, treatment began at 250 mg/m$^2$, but eventually was lowered to 170 mg/m$^2$, and for patients with poorer performance status, 135 mg/m$^2$. More than a third of patients had liver involvement, and 50 percent presented with bulky tumors. All had prior platinum-containing chemotherapy; 19 had prior radiation.

Results: 9 partial responses and 1 complete response, for a 22 percent response rate. In patients whose tumor had continued to grow while on platinum regimens, taxol resulted in a 14 percent response rate.

Median duration of response was 7.2 months; 6 percent of patients have survived for more than two years.

▶Albert Einstein protocol 012, 32 patients, receiving 200 to 250 mg/m$^2$. Liver involvement in more than a third of patients, but 87 percent of all patients were ambulatory. A quarter of patients had bulky tumors. All but two patients had prior chemotherapy.

Results: 4 partial responses and 2 complete responses, for an overall response rate of 19 percent. In one patient, the tumor completely disappeared. Of patients who were refractory to platinum, 16 percent responded to taxol.

However, all patients relapsed. Median duration of response was 8.7 months, survival was 6.5 months, though some patients have lived longer than two years.

▶Gynecologic Oncology Group protocol 014, 46 patients receiving 170 to 135 mg/m$^2$, generally good

**THE CANCER LETTER**

*Editor:* **Kirsten Boyd Goldberg**
*Associate Editor:* **Paul Goldberg**
*Founder & Contributing Editor:* **Jerry D. Boyd**

**PO Box 15189, Washington, DC 20003**
**Tel: (202) 543-7665 Fax: (202) 543-6879**

Subscription rate $215 per year North America, $240 elsewhere. ISSN 0096-3917. Published 48 times a year by The Cancer Letter Inc., also publisher of The Clinical Cancer Letter. 

performance status. Liver involvement in one-fifth of patients, bulky tumor in 42 percent. All had prior chemotherapy.

Results: 9 partial responses and 5 complete responses, for a 31 percent response rate. In platinum refractory patients, response rate was 21 percent. Median duration of response was 7.5 months; all patients relapsed. Median survival was 15.9 months.

▶NCI Medicine Branch protocol 011, a phase 1 study with 15 patients, testing doses from 170 to 300 mg/m$^2$ with G-CSF support. One-fifth of patients had liver involvement and bulky disease was present in 28 percent of patients. All had prior chemotherapy.

Results: 4 partial responses and 2 complete responses, for a 40 percent response rate. Sixty-seven percent of the platinum-refractory patients responded to taxol. Median duration of response was 6 months; median survival was 19.6 months.

▶NCI Medicine Branch protocol 028, a phase 2 study with 50 patients testing doses from 170-250 mg/m$^2$ with G-CSF support. A third of patients had liver involvement, 44 of patients had bulky disease.

Results: 17 partial responses and 1 complete response, for a 36 percent response rate. Forty percent of the platinum-refractory patients responded to taxol. Median duration of response was 6.8 months, and median survival has not yet been reached.

In the two NCI trials, responses were seen in good performance patients as well as in patients who had received up to four prior chemotherapy regimens.

Canetta concluded that the trials demonstrated consistent objective response rates, and there were complete responses in each of the trials. Overall, 25 percent of platinum-refractory patients responded to taxol.

Responses were higher in patients with the higher starting doses; however, Canetta said selection bias could account for the results. Patients with better performance status generally were given higher doses.

Median response ranged from six to eight months, and duration of response by starting dose was not statistically significant.

Survival ranged from 6 months to 11.1 months, however, the survival figure in the NCI phase 2 study has not been reached. The literature review found that survival for metastatic ovarian cancer in patients receiving other therapies is about six months, Canetta said.

The dose-limiting toxicity of taxol is neutropenia, said Nicole Onetto of BMS. Safety data was collected on 655 patients. Since patients receiving taxol began getting premedication for hypersensitivity, that adverse event is less of a problem. Premedication consists of dexamethasin, antihistamine and an $H_2$ blocker. Extensive cardiac data was collected, but events are generally asymptomatic and general cardiac monitoring is not recommended. Taxol has clinical tolerance at doses from 151-190 mg/m$^2$, Onetto said.

**NCI Compassionate Use Protocol**

NCI's Susan Arbuck presented the Institute's Treatment Referral Center protocol 9103, for compassionate treatment of patients who had failed three prior chemotherapy regimens for ovarian cancer. The eligibility was changed last July to two prior regimens.

The protocol was begun to provide access to taxol and to gather data; 43 cancer centers participated. Treatment was 135 mg/m$^2$ by 24 hour infusion every three weeks. G-CSF was given in subsequent cycles under certain conditions.

The protocol enrolled more than 2,500 patients. Arbuck limited the data presented to 500 patients. One-fifth of patients had liver involvement; 39 percent of patients got G-CSF, 42 percent received a reduction in taxol dose. Median number of courses per patient was five.

There were life-threatening infections in 5 percent of 450 patients. In the first 480 patients, there were eight treatment-related deaths, for a death rate of 1.6 percent. Deaths occurred after the first course of therapy.

Of 348 patients evaluable for response, the partial response rate was 20 percent, while the complete response rate was 4 percent. Median time to progression was 7 months; median survival was 9 months.

Arbuck emphasized that this is a high response rate for such heavily pretreated patients, and taxol was administered safely at the cancer centers.

**FDA: No Objection To Data**

FDA's Williams said the agency had "no objection with the data presented," and complimented BMS and NCI for "bringing data to us so quickly when it became apparent that this was a unique drug." It was only four months from the time of the NDA submission to FDA's review.

"The view that we wait for a pile of documents to fall on us and then we say, No--that's not the way we do business," Williams said.

Williams said he considered the Hopkins and GOG trials the most relevant for the question of dosage. Those two trials used the 135 and 170 mg/m$^2$ doses, and have complete and verified data. The Einstein and NCI Medicine Branch protocols used the higher doses, and, while the NCI Treatment Referral Center protocol used the lower dose, the data is not complete

and verified. However, Williams said the TRC protocol "did a remarkable job getting response data on patients who would really be getting this drug."

**Taxol History**

Taxol was discovered in 1962 during an NCI natural products collecting expedition in the Western states. The drug structure was described in 1970 by Monroe Wall and M.C. Wani of Research Triangle Institute.

The agent's mechanism of action as a microtubulin inhibitor was first described in 1979 by Susan Horwitz of Albert Einstein School of Medicine.

NCI began clinical trials of taxol in 1983 and later sought private sector partnership for the drug's development. Bristol-Myers Squibb competed for and won the Cooperative Research ,and Development Agreement for taxol in 1991. BMS also entered into agreements with the U.S. Forest Service and the Bureau of Land Management on yew bark supply.

BMS and NCI are supporting research on chemical synthesis of taxol, and the company has said it expects to rely heavily on chemical sources of the drug within two to three years.

This fall, NCI expanded access to taxol for ovarian cancer patients, and announced that a new protocol is available to NCI-designated comprehensive and clinical cancer centers for treatment of advanced breast cancer patients.

To be eligible for the breast cancer protocol, a patient must have failed two prior chemotherapy regimens and be refractory to doxorubicin. Physicians wishing to enroll patients may contact the closest NCI-designated cancer center or call the Treatment Referral Center at 301/496-5725.

## ACS, In Major Restructuring, Forms New Executive Committee, Bylaws

The American Cancer Society, wrapping up what new Executive Vice President John Seffrin called "four and a half years of change and instability," has completed the first significant revision in its governance structure since 1945 as well as reorganization of its national office.

The governance changes were given final approval at the ACS annual meeting in Atlanta earlier this month, when the House of Delegates voted itself out of existence and merged its members into the Board of Directors. A new Executive Committee was established which will oversee the Society's operations between meetings of the board and will be responsible to the board. The number of standing committees were reduced from 23 to 16, and the number of appointed groups were cut from 120 to 56. All committee actions, including those of the Executive Committee, are subject to review and reversal or modification by the full board.

Each of the Society's 57 divisions will be represented on the board by at least two members, with the larger divisions having more.

Reorganization involving the senior national staff was announced by Seffrin at the annual meeting, including his decision to operate his office as a "troika" with two deputy executive vice presidents. He has already hired one--Richard McGuinness, who has been executive vice president of the Connecticut Div. His title in the national office will be deputy EVP for operations.

The third member of the troika will be deputy EVP for research and medical affairs.

Four of the seven senior vice presidents have new or modified areas of responsibility:

▶James Bell, who was senior vice president for finance before becoming acting EVP last year, is now senior advisor to the office of the executive vice president and senior vice president for support services.

▶Gerald Murphy, who has been group vice president for medical affairs and chief medical officer, now is senior vice president for medical affairs.

▶Allan Erickson, who has been senior vice president for public education and special programs, is now special assistant to the executive vice president and senior vice president for total quality performance.

▶Harry Linduff, who has been senior vice president for human resources, is now group vice president for division services.

John Laszlo remains as senior vice president for research; Michael Herron as senior vice president for communications; and John Montgomery as senior vice president for income development.

ACS is working on the next level of reorganization, which will include the 25-30 vice presidents and department heads.

**Opposition To Changes**

The restructuring was not without controversy. Delegates and board members had two final opportunities to debate the changes, at a Reference Committee forum and the final vote the following day. Helene Brown, past officer director, led the opposition. The Reference Committee meeting was attended by a majority of delegates and board members.

Brown objected to the provisions which grant the Executive Committee all the powers of the board, contending that the board could not legally transfer its responsibilities to another body. Acknowledging

that the board could review and overturn actions of the Executive Committee, she pointed out that since the new bylaws do not mandate more than one meeting of the board a year, overturning actions taken months before might not be feasible.

Brown called for a legal opinion on whether the board could delegate its responsibilities. She got one immediately from Francis Wilcox, former board chairman and an attorney. Wilcox did not offer an opinion on the legality of the new bylaws but did agree with Brown that "over ruling an action six months later is not practical. It is not a proper way to run the Society. Any action on programs and policy should be acted upon by the board."

Gerald Dodd, immediate past president, noted that the new bylaws require final approval of the annual budget by the board and suggested that the Executive Committee, as the Society's operational overseer, would be limited in the substantive actions it could take.

Brown responded that "the boards of savings and loans are now being hammered to death because they had the responsibility and didn't know what was going on." She suggested that "this huge issue can be resolved easily by having the board meet three times a year and the Executive Committee meet three times a year."

Brown further argued that having the Finance Committee report to the Executive Committee rather than the board, as called for in the new bylaws, "is wrong. All action items of the committees should go directly to the board."

Gerald Mueller, director at large, said "there is a strong argument for Helen's point of view. Subsequent reviews of an item are not always presented in the same way, in the same context."

Reference Committee Chairman Robert Eyerly called for a show of hands on the issues raised by Brown, Wilcox, and Mueller, and about 80 percent of those present indicated support for their positions.

When the proposed bylaws were presented to the full House of Delegates the next day, however, the changes recommended by the Reference Committee did not address some of the key points made by Brown, primarily whether committees would report to the Executive Committee or board. The Reference Committee did recommend increasing the number of board meetings to two, and decreasing the required number of Executive Committee meetings from four to two.

Wilcox objected to the omissions, but Eyerly responded that "I thought the emphasis was on the reporting time taking six months. We cut out the six month lapse" by changing the frequency of meetings."

Brown disagreed. "It is the stewardship of the Society that is at issue. It was the overwhelming opinion of those present at the Reference Committee yesterday that the stewardship remain in the hands of the board."

Charles Osburn, who cochaired the working group that drew up the bylaws proposals, said that "we've been looking at this for years. We have a form of governance that streamlines the organization, an Executive Committee that handles operational functions."

Delegate Paul Dvorak had the last word on the issue. "The Reference Committee report this morning does not reflect the straw vote taken yesterday. This is an example of what can happen when things are filtered through another group."

That view did not prevail, however. When the vote was taken on approval of the new bylaws, the vote was overwhelmingly in favor, the House of Delegates voting itself out of existence and the reorganization of the Society's governance complete.

Under the new bylaws, the Executive Committee consists of the current and immediate past president, vice president, chairmen and immediate past chairman of the board, vice chairman, treasurer, secretary, chairmen of the major committees--all of whom are members of the board--and 10 additional board members elected by the board.

The total of 30 Executive Committee members is to be divided equally between medical and lay members.

**Medical Examiner Requirement**

Another issue that generated controversy was a bylaws change requiring that the vice chairman of the Committee on Research and Clinical Investigation be a medical member. Kathleen Horsch, current chairman of that committee, pointed out at the Reference Committee meeting that policy has been for both the chairman and vice chairman to be lay members. That makes less likely any potential conflict of interest when the committee reviews and approves or rejects research grant applications, one of its primary functions.

Mueller supported Horsch's position. "The system works. Also, when you have both the chairman and vice chairman on the lay side, it is an excellent opportunity to educate the next chairman."

President (now past president) Walter Lawrence argued that the intent of the change was to "encourage the partnership of our lay and medical members by sharing responsibility."

Those present at the Reference Committee meeting

voted solidly in support of the change, accepting Lawrence's argument. However, the committee in its deliberations after the meeting went along with Horsch and recommended that the bylaws revert to the previous requirement.

Osburn, whose bylaws working group had agreed with other Reference Committee recommendations, disagreed with that one.

"We were not persuaded by the potential for conflict of interest," he said. The new provision was left intact when the House of Delegates gave final approval to the final new set of bylaws.

For the purpose of distinguishing between medical and lay members, the bylaws define "medical profession" as doctors of medicine, dental medicine, dental surgery, osteopathic medicine, philosophy in the biological sciences, and science; and nurses, pharmacists, and social workers with at least a master's degree.

## ACS Cheers Tobacco Tax Rise In Mass. Victory At Polls

Whether they had voted for President Bush or Gov. Clinton, American Cancer Society board members, delegates, and staff exuded the post election glow of success at their annual meeting in Atlanta earlier this month. They had won a significant victory at the polls in one state, when Massachusetts voters approved a 25 cent per pack increase in the state's cigarette tax, bringing the total to 51 cents.

"We went head to head with the tobacco industry," said Blake Cady, president of the ACS Massachusetts Div. He suggested that the success there and the big cigarette tax increase enacted by California voters four years ago should encourage "us to tackle the tobacco industry head on nationally."

Cady said the tobacco industry spent $10 million to defeat the initiative, "twice what they spent in California. They know now what it means."

The Massachusetts Div. spent $110,000 in cash and about $200,00 in in-kind services. However, "we would not have won without the support of the American Cancer Society national office." Late in the campaign, national contributed $250,000 for paid advertising which Cady said turned the tide.

"It was a superb campaign," said Michael Pertschuk, member of the Committee on Tobacco and Cancer. "It benefitted tremendously from the serious support of ACS. This goes back to Alan Davis making (increased cigarette taxes) an issue."

Davis, ACS vice president for public issues, is the current chairman of the National Coalition on Smoking or Health, which consists of ACS, the American Heart Assn., and the American Lung Assn. He has suggested that the coalition should undertake the effort of selling Congress on raising the federal excise tax on cigarettes to as high as $5 per pack.

"The time has come to raise cigarette excise taxes by a massive amount," Davis said. "We've mentioned $5, and that does get attention." When members of the coalition meet Nov. 30, they will be asked to adopt that as a national priority, Davis said. The first goal is to decrease the access of young persons to cigarettes, which occurs dramatically when there is a substantial increase in the cost of a pack. The second goal is "the enormous revenue that can be derived."

In Canada, where cigarettes cost as much as $8 a pack (about $5 in taxes), there has been a decrease of 36 percent in young smokers since the huge tax increase went into effect. In California, since the 25 cent increase in 1988, the number of young smokers has declined by 17 percent.

Davis said that an increase of $2 to $3 in the tax would generate from $60-70 billion in revenue.

**Anger Over NIH Alternative Therapy Office**

Elation over the Massachusetts election turned to outrage when ACS board members discussed the NIH office for "alternative" therapy (**The Cancer Letter**, Oct. 9). They were incensed that the office is spending $2 million this year.

ACS board members said they were offended by the recent decision of NIH to substitute the word "Alternative" for "Unconventional" in the name of the Office for the Study of Unconventional Medical Practices. Also, the board said, NIH agreed to waive conflict of interest rules, which permits advocates and practitioners of unconventional methods, who may benefit financially from the publicity and possible wider use of those methods, to serve as official, paid consultants to the government as members of the office's advisory panel.

Henry Lynch said the office is charged with looking into unconventional methods for treatment of cancer and other diseases. He suggested forming a coalition of heart, lung, and arthritis organizations to deal with the issue. "Those diseases are where all the quacks hang out," Lynch said.

Helene Brown reviewed the history of the office, which was established when Sen. Tom Harkin (D-IA) inserted it into the FY92 appropriations bill. Harkin had been lobbied by a former congressman, Berkley Bedell, of Iowa, whose prostate cancer was treated by an unconventional practitioner.

"Undoubtedly we will have a new secretary of Health and Human Services," Brown said. "I think we

can get a political solution without getting up a coalition."

The ACS Committees on Public Issues and on Questional Methods of Cancer Management will work together on the issue.

### ACS Budget Squeeze

Budget squeeze: In the current fiscal year, ACS has projected that it will be able to fund only nine percent of new grant applications. Only 12 to 13 percent of competitive grants will be funded. And, worst of all, only one in 11 first time applications from young investigators will be funded.

Henry Pitot, member of the Research and Clinical Investigations Committee, noted that the American Heart Assn. allocates 30 percent of its funds to research (ACS is spending 25 percent on research this year). "We should look at this carefully, and do some soul searching about our funding of young investigators," Pitot said.

Larry Fuller, ACS vice chairman and chairman elect, said that in the past, the allocation to research has been as high as 30 percent. However, the percentage went down as more money was raised, with the result that research was still getting more money each year. The percentage estimated for this year does not include amounts which will be used to fund the "pay if" grants should income exceed projections.

## DCE To Provide $3.4 Million For DES Followup; Board Ok's Other Initiatives

NCI's Div. of Cancer Etiology plans to provide $3.4 million over the next four years to support the follow-up of patients identified with clear cell adenocarcinoma as a result of exposure to diethylstilbestrol (DES).

The DCE Board of Scientific Counselors gave concept approval to the proposed new RFA, which will support investigators and organizations that have participated in the documentation of the DES cases.

Nearly 600 women with CCA of the cervix or vagina associated with DES exposure have been reported to a registry established by Arthur Herbst. An estimated 20 new cases and 10 to 15 recurrent cases of CCA are diagnosed annually in the U.S. In the Herbst registry, 90 percent of newly diagnosed patients have stage 1 or 2 disease. Ten-year survival for stage 1 disease is 90 percent with conventional therapy.

The board, at its meeting last month, turned down a concept for an RFA on rodent models of malignant mammary tumors on a 9-2 vote with one abstention. Board members said they were concerned about the proposed RFA's funding of $1 million per year ($4 million total) for research that only indirectly concerned human tumors. Board members said they wanted more emphasis on human cancer when possible.

Following are the concept statements:

**Followup of patients with DES-associated clear cell adenocarcinoma.** Proposed RFA, cooperative agreements, first year funding $850,000, total $3.4 million over four years. Program coordinator: Iris Obrams, Epidemiology & Biostatistics Program.

Objectives of this proposed cooperative agreement are:

1) to continue followup of documented clear cell adenocarcinoma (CCA) patients and continue accrual of incident cases to further define the age-incidence curve, the survival rate, the recurrence rate, the incidence of second primary cancers, and the incidence of other health outcomes;

2) to ascertain data on exposure to DES, other hormones, and other relevant factors, and to assess the determinants of survival, recurrence, and other health outcomes in women with CCA.

Investigators and organizations that have participated in documentation of cases of CCA, with data on treatment, and systematic followup for health outcomes, will be encouraged to respond to this RFA and to participate in cooperative studies of CCA. These studies may include assessment of the completeness of case identification, confirmation of diagnosis, validation of data on DES and other hormonal exposures, evaluation of health status, and gathering of information useful for future followup.

Utilization of existing CCA registry data can be maximized through:

1) Development of a mechanism to permit access to specimens, serum, and leukocytes from vaginal and cervical CCA patients. This would facilitate molecular studies on archival specimens from CCA patients where serial biopsies are available, development of a transplant derived cell line of CCA to permit in vitro testing of steroid receptors and drug sensitivity, and genetic studies of family members of patients with DES associated malignancy, in order to define molecular markers of carcinogenesis.

2) Establishment of consensus as to reasonable guidelines for the primary treatment of CCA patients aimed at more conservative surgical approaches and morbidity reduction.

3) Studies of the emotional effects of DES exposure in survivors of DES associated vaginal CCA, including coping mechanisms, body image, sexuality, and transgenerational relationships.

**Human T-cell lymphotropic virus-induced diseases: protective immune responses and potential for vaccine development.** Proposed RFA, $500,000 per year, four years, total $2 million. Program director: Padman Sarma, Biological Carcinogenesis Program.

Goal of this proposed RFA is to stimulate HTLV research related to vaccine development efforts that will eventually lead to the vaccine prevention and control of HTLV induced diseases. Specific examples of such studies include, but are not limited to: 1) development and use of HTLV animal models suitable for vaccine related studies, 2) elucidation of specific mechanisms of protective immunity against infection with HTLV, such as the immunity elicited in rabbits against HTLV infected cells through the intravenous administration of hyperimmune globulins directed against HTLV (passive immunity), 3) development of vaccination strategies to elicit mucosal immunity in the naturally occurring STLV primate animal models, 4) characterization of host protective immune responses to define the relevance of regional immunity, 5) definition of protective immune responses to

synthetic peptides and conformation dependent epitopes, 6) characterization of specific B and T-cell immune responses to natural or experimental infections with HTLV-1 and HTLV-2, 7) identification of viral epitopes responsible for inducing protective immunity, 8) development and evaluation in animal models of immuno-prevention approaches to elicit active or passive immunity with the aims of preventing primary infection and disease development, the approaches include the use of vaccines directed against specific viral structural components and/or products of regulatory genes, tax and rex, and the administration of hyperimmune gamma globulin to elicit passive immunity, 9) investigation of the emergence of viral variants/defective virus capable of evading the immune system in humans chronically infected with HTLV-1, 10) analysis of cross protection between HTLV-1 and HTLV-2 and other variants, 11) development of standardized assay procedures for accurately quantitating infectious virus and virus-neutralizing antibodies.

**Interactive research project grants for interdisciplinary studies in the genetic epidemiology of cancer.** Proposed as a program announcement, but changed to an RFA at request of the board. Annual amount up to $2 million. Program director: Daniela Seminara, Epidemiology & Biostatistics Program.

The goal of this initiative is to encourage collaborative and interdisciplinary genetic epidemiology investigations to evaluate the interaction of genetic and environmental factors in cancer etiology. This initiative uses the Interactive Research Project Grants mechanism. The exchange of data, materials and ideas is the primary requirement. Requests for limited shared resources may be proportionally budgeted into each application.

Inter-institutional collaborations between epidemiologists, laboratory scientists, clinical oncologists and geneticists, epidemiologists, biostatisticians and experts in related disciplines working on the same cancer site/syndrome are encouraged.

Projects will be evaluated on the potential for their results to be translated to cancer prevention and control. Particularly encouraged are studies of breast, ovarian, lung, prostate and uterine cancers. Components of collaborative proposals could include, but not be limited to:

--Ascertainment of cancer prone families from large, population based samples, and creation of extended multigenerational pedigrees with the establishment of related epidemiological data bases and blood/tissue specimen repositories.

--Studies in inherited variation in genetic susceptibility to environmental carcinogens, and, conversely, studies to determine the mode of inheritance of susceptibility to malignancies with known environmental or endogenous risk factors.

--Studies of loss of heterozygosity in tumors, to suggest candidate regions for cancer related genes and to define etiologic subgroups.

--Development and validation of novel statistical models to evaluate gene/environment interactions, genetic heterogeneity and alternative modes of inheritance (e.g. gene imprinting) within existing cohort or family datasets.

--Feasibility and validation studies to test the applicability of developing experimental laboratory techniques to genetic epidemiology investigations.

--Pilot studies to test innovative hypotheses on the molecular mechanisms underlying the genetic components of cancer etiology using the biological resources made available through family and case control studies.

--Genetic epidemiology studies of precancerous lesions in familial clusters, including the analysis of heritable and environmental factors affecting the progression of the precursor state to malignancy.

--Studies to evaluate the impact and effectiveness of predictive genetic testing among groups of high risk individuals and their families.

**Interdisciplinary training program in the genetic epidemiology of cancer.** Proposed program announcement. Program directors: Daniela Seminara, DCE Epidemiology & Biostatistics Program; and Vincent Cairoli, Cancer Training Branch, Div. of Cancer Biology, Diagnosis & Centers.

Objective of this concept is to establish a comprehensive research training program in the genetic epidemiology of cancer accessible to investigators at different stages of their scientific careers. The goal is to provide students, young investigators, and established researchers interested in diverse aspects of the genetic epidemiology of cancer with new research skills and a breadth of expertise that encompasses the many disciplines now merging into this expanding field. A second goal is to promote the development of the inter- and intra-institutional infrastructure for providing training in the genetic epidemiology of cancer that could be accessible to interested investigators at different stages of career development.

Applications will be accepted for institutional National Research Service Awards (T32 grants), NRSA awards for individual senior fellows (F32 grants), and Education Projects for Short Term Training Courses (R25 grants).

**Procurement of transformed lymphocytes, lymphoblastoid lines, and DNA for genetic linkage studies.** Recompetition of a contract held by American Type Culture Collection, total $1.3 million over four years. Project officer: Neil Caporaso, Family Studies Section.

The Family Studies Section of the Environmental Epidemiology Branch needs support in ongoing genetic studies of cutaneous melanoma, nevoid basal cell carcinoma, neurofibromatosis type 2, Hodgkin's disease, Li-Fraumeni syndrome, chronic lymphocytic leukemia, and cancers of the lung, breast, ovarian, and bladder.

The contractor will provide all laboratory and support personnel to process up to 800 samples per year. Samples from case-control studies require DNA extraction from the fresh whole blood. For samples from cancer families planned for linkage analysis, lymphocyte transformation, bulk growth of cells to 1 gram quantities and then extraction of DNA (with an aliquot of lymphoblastoid cells saved for future use) is performed.

**Support services for biostatistical and analytical studies.** Recompetition of contract held by Westat Inc., total $6.463 million, four years. Project officer: William Blot, Biostatistics Branch.

This project will provide support services for methodologic and field studies of cancer etiology undertaken by the Biostatistics Branch alone or in collaboration with other investigators in the U.S. and abroad.

Support services include development of liaison with organizations and individuals at a local or international level whose cooperation is needed for the conduct of a study; assistance in design and pilot testing of forms required to conduct field investigations; hiring, training and supervision of technical personnel; collection of required data; data reduction activities involved in field investigations; and management of data flow.

**The board** also gave concept approval to: addition of $700,000 to a study between NCI and the Children's Cancer Group on electromagnetic fields and childhood leukemia; and a two-year continuation of contracts with Northern California Cancer Center, Univ. of Pennsylvania and Westat Inc. worth $1 million total to complete a case-control study of cutaneous malignant melanoma.