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NCI Agrees To Give NSABP One Year Until Recompetition; Advisors OK Concept

An NCI advisory board this week approved the concept for recompetition of the National Surgical Adjuvant Breast & Bowel Project.

The action by the Div. of Cancer Treatment Board of Scientific Counselors set a deadline of Nov. 15, 1995 for applications for the five-year, $48 million grant to run the cooperative group.

In a related development, the Univ. of Pittsburgh, which currently administers NSABP, has begun formal recruitment of candidates for chairman of the group (see related story, page 4). The new chairman, who is to be elected by Sept. 1, will have a year to prepare a grant application.

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In Brief

William Blot, Michael Grever, Others To Leave NCI; RAC Approves Naked DNA Vaccine Trial

WILLIAM BLOT, chief of the Biostatistical Branch in NCI's Div. or Cancer Etiology; **CORA SUIT**, administrative officer for the Epidemiology & Biostatistics Program; and **THOMAS NIGHTINGALE**, program director in the extramural Biological Carcinogenesis Branch, will soon follow DCE Director **Richard Adamson** into retirement. Adamson announced last week he would retire Aug. 31 after 33 years with NCI, 14 of them at the helm of the division.... **LUCY ANDERSON** has been named acting chief of DCE's Laboratory or Comparative Carcinogenesis. She replaces **Jerry Rice**, who was appointed in April as director of Frederick Cancer Research & Development Center. . . . **MICHAEL GREVER**, director of the Developmental Therapeutics Program in the Div. of Cancer Treatment since 1990, is leaving NCI to become a professor of medicine at John Hopkins Univ. Grever came to NCI from Ohio State Univ. in 1989 as deputy director of DCT. He supervised the emergency Taxol acquisition program, the initiation of cell line screening and the establishment of in vivo models, the development of computer programs for handling screening information, the opening of the NCI's natural products repository and other innovative projects. "He was a unique leader for DTP, combining a strong commitment to drug discovery and a knowledge of and faith in clinical drug trials," DCT Director **Bruce Chabner** said this week. . . . **DAVID CURIEL**, Univ. of Alabama at Birmingham Comprehensive Cancer Center, has received approval from the NIH Recombinant DNA Advisory Committee to conduct the first study of a naked DNA vaccine in humans. The trial will be conducted in patients with metastatic colorectal cancer.

NSABP Recompetition Planned For Fall Of 1995, Award In 1996

(Continued from page 1)

"All parties have agreed to accept this process," Bruce Chabner, DCT director, said to the board. "We have agreed to give NSABP a full year from the time of election of a new chairperson to submit the grant."

A Request for Applications is expected to be issued this fall, with a Nov. 15, 1995, due date for applications. Funds would be awarded in January 1996.

Chabner earlier had suggested a recompetition that would award the grant in 1995. Sources in NCI said that that timing was unrealistic, considering it can take a cooperative group a year to write a strong grant application.

Separate Statistical Competition?

The NSABP chairman to be elected this summer will have responsibility for the group headquarters and operations center, for continuing the trials and writing the grant application.

If the new chairman does not stay with the Univ. of Pittsburgh, NCI will not oppose the move, sources said to **The Cancer Letter**. NCI's primary concern is that there be no further disruption in NSABP trials.

It is possible that there could be a separate competition for the group's statistical center, sources said. Under former NSABP chairman Bernard Fisher, the chairman chose the statistical leader from the Univ. of Pittsburgh.

NCI sources emphasized that the competition for the grant will be open and that the Institute expects there to be more than one application.

A successful candidate to take over the NSABP would have to assure NCI that all current trials and followup on previous trials would continue seamlessly, sources said.

Fran Visco, member of the President's Cancer Panel and president of the National Breast Cancer Coalition, urged the board to ensure that consumers have "a seat at the table" on every cooperative group committee.

Excerpts from the concept statement follow:

Cooperative Group for Therapeutic Studies of Breast and Colorectal Cancer in Adults. RFA, U10 cooperative agreements, first year award $9.6 million, five years.

NCI is seeking a surgically oriented, multi-disciplinary and multi-institutional team of talented scientists from academic and community medical centers who will interact with the Cancer Therapy Evaluation Program staff to conceive, create, and evaluate new approaches to the treatment of breast and bowel cancers. Furthermore, in view of the focus on breast cancer, NCI is encouraging this group to include women scientists, who are recognized experts, in positions of both scientific and administrative leadership.

Although new treatment ideas will come from diverse arenas such as industry and single-institution trials, NCI wishes this group to also encourage and foster the development by its membership of original phase I and II trials that can potentially serve as a basis for phase III comparisons. Scientific approaches should be broad and reflect the creativity and capabilities of team participants, including surgical, medical, radiotherapeutic, laboratory, diagnostic imaging, and statistical skills. Team objectives and approaches will be investigator-originated but consistent with program aims of improving the survival and quality of life for persons with breast and bowel cancers or those at risk for these diseases.

Cooperative groups consist of researchers who jointly develop and conduct cancer treatment clinical trials in multi-institutional settings. They are a major component of the extramural research effort of the Div. of Cancer Treatment. Each group is supported to continually generate new trials compatible with its particular areas of interest and expertise, as well as with national priorities for cancer treatment research. Unlike most other major NIH cooperative clinical trials efforts, group structure and funding are not limited to any specific clinical trials. This mechanism thus has the potential for considerable flexibility in resource allocation and for the rapid testing of promising new cancer therapies in large patient populations.

Highlighting surgical expertise can facilitate innovative surgical treatment such as laparoscopic abdominal surgery and breast-sparing approaches, and the group also provides for the inclusion of medical

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"gatekeepers" who are ideally suited for participation in early detection, diagnostic, and preventive strategies. In addition, the participation of surgeons will ensure that adequate tissue and serum will be supplied for tumor banking, which will be required in most future adjuvant trials.

Examples of possible innovative therapeutic and preventive approaches include enhanced diagnostics via digital mammography and breast magnetic resonance imaging; tumor vaccines that express CEA and monoclonal antibodies against the her2-neu antigen; exploration of retinoids, vitamin D analogs, and other differentiating agents; testing of new chemotherapeutic agents such as topoisomerase I inhibitors, taxanes, thymidylate synthase inhibitors, edatrexate, and navelbine; development of pilot trials using intermediate endpoints for prevention of breast and bowel cancer; and exploration of critical markers that indicate treatment sensitivity or resistance and detection of genetic precursors in high-risk individuals.

Applications for such a cooperative group must respond to the following criteria: 1) documented ability of the membership to accrue large numbers of patients with all stages of resectable breast and colorectal cancer, 2) demonstration of scientific leadership in these diseases including both clinical and laboratory expertise, 3) provision for a statistical office with leadership that has proven experience in conducting and analyzing phase I-III clinical trials (the organization of this statistical unit should take into account and provide plans for continued followup of patients entered onto selected ongoing NSABP trials), 4) organization of a quality assurance program that emphasizes productivity as measured by both adequate accrual and high-quality record-keeping (this aspect must include plans for an auditing system, an independent data monitoring and safety committee, and inclusion of lay advisors and consumer advocates, where appropriate), 5) development of a tumor banking system that facilitates integration of correlative studies into the overall research effort, 6) detailed methods for assuring inclusion in these trials of adequate numbers of women and minorities according to NIH guidelines.

The DCT board also gave unanimous concept approval to recompetition of a contract for the provision of tumor-infiltrating lymphocytes for the DCT Surgery Branch. The board had cut Branch Chief Steven Rosenberg's funding request a year ago and asked him to return to the board with additional data.

Board members, commenting that they were impressed with recent results of trials with TIL, restored Rosenberg's funding. The concept statement follows:

To Provide Tumor-Infiltrating Lymphocytes for Therapeutic Administration in Patient Protocols. Recompetition of a contract held by OTC Biotechnology Research Institute, total $2,994,875 over three years.

Studies in patients with metastatic melanoma demonstrated that TIL localized to sites of tumor after adoptive transfer. The studies suggested that administration of cyclophosphamide pretreatment improved TIL localization to tumor. In addition, these patient trials demonstrated that approximately 40 percent of patients could respond to TIL and systemic IL-2, despite the failure of previous treatment with IL-2 alone in many cases. Preclinical models showed that the release of cytokines by these TIL was related to their in vivo efficacy.

Surgery Branch efforts that require large volume lymphocyte culture for patient administration fall into several areas:

1. The impact of cyclophosphamide administration of TIL traffic and the incidence and duration of response to treatment with TIL and IL-2 have not been definitively determined. To answer this question, the Branch will institute a prospective randomized trial of patients receiving TIL and IL-2 that will involve randomization to receive or not receive cyclophosphamide. In this trial, the traffic of TIL will also be studied to determine the impact of cyclophosphamide administration on TIL traffic. Prospective studies of the properties of TIL such as phenotype, lytic specificity, and specific cytokine release will be performed to attempt to identify in vitro correlates of in vivo effectiveness.

2. A protocol inserting the gene for human tumor necrosis factor alpha into TIL is underway, testing the hypothesis that TIL could serve as a local delivery vehicle for TNF-alpha based on their tumor-homing properties. TNF was selected based on preclinical murine TIL models in which the TNF secretion appeared to be a necessary capability of TIL with in vivo efficacy. In addition, recent clinical studies in the Branch and elsewhere using TNF at high doses in isolated limb perfusion have shown that TNF does have significant antitumor activity against melanoma and sarcoma. It appears that achieving high local tumor concentrations of TNF without systemic toxicity was the obstacle in previous TNF clinical trials. Presently, the efforts to obtain high levels of TNF secretion by TIL transduction are proceeding using new high-titer, hypersecretor retroviral vectors for transduction.

3. Other efforts will involve unmodified TIL studies in patients with metastatic breast cancer, colon cancer and renal cell cancer. Preliminary in vitro studies suggest that a proportion of these tumors can produce TIL that show autologous tumor recognition, measured either by cytolysis or cytokine release. Pilot phase II efforts treating patients with these other tumors will be pursued. Current

plans are to treat 10 to 15 patients with each histology using TIL and high-dose IL-2 in order to determine if responses are seen.

4. For patients who are unable to generate therapeutically effective T cells, other efforts are underway to modify those patients' tumors and utilize them in immunization strategies. Current protocols underway introduce the gene for TNF or IL-2 into patient tumor lines followed by autologous immunization and subsequent harvest of DLNL to be expanded in vitro. Approval has been obtained from the Recombinant DNA Advisory Committee and FDA to treat patients in this protocol. These pilot trials in a very limited number of patients are underway, and lymphocytes for treating these patients will be expanded in Surgery Branch laboratories and not at the contract facility. If promising results are seen in pilot trials, lymphocytes may be grown for a small number of patients (<10) at this contract facility.

These efforts require the ability to generate large numbers of T cells in culture for patient transfer. Murine models show that antitumor response is directly related to the number of TIL transferred. In a typical treatment course for a patient receiving TIL, the in vitro culture process takes approximately six weeks, and the final culture is contained in 160 liters. Fixed material costs for the final culture expansion at the contractor are approximately $9,000 for a typical treatment course. The current contractor uses a facility of about 900 square feet and a staff of 4.5 dedicated to this project. Thus, under current conditions and with ongoing work, the number of patients treated is maximized under the current budget.

Univ. Of Pittsburgh Seeks Senior Surgical Oncologist

The Univ. of Pittsburgh has begun a search for a senior surgical oncologist to lead breast and colorectal cancer clinical trials.

The following announcement was submitted to **The Cancer Letter** last week:

The Univ. of Pittsburgh Medical Center and the Pittsburgh Cancer Institute are seeking a senior surgical oncologist with expertise in clinical investigations and clinical trials to assume a faculty position at the rank of Professor-Associate Professor in the Department of Surgery. The faculty member will also assume responsibility as Director of the PCI's Breast Cancer or Gastrointestinal Research Program and may have an additional broader responsibility for large scale, multicenter clinical oncology trials.

Interested applicants should send, as soon as possible, a letter and curriculum vitae to Thomas Detre, MD, Senior Vice Chancellor, Univ. of Pittsburgh Medical Center, via fax at 412/624-1881.

Breast Cancer Prevention Trial Should Resume, ODAC Says

FDA's Oncologic Drugs Advisory Committee voted unanimously last week to permit resumption of the suspended study of tamoxifen as a breast cancer preventive in healthy women at greater risk for the disease.

The Breast Cancer Prevention Trial, which NCI suspended in April, will be allowed to proceed despite evidence accumulated since the start of the study in 1992 that postmenopausal women who take tamoxifen (Nolvadex, Zeneca Pharmaceuticals) have a higher risk of endometrial cancer then those in the general population.

The NCI-funded study has estimated that the drug could prevent 133 cases of breast cancer in 8,000 women, reducing their risk by as much as 50 percent, but that 83 women might develop endometrial cancer.

Inconclusive Results On Complications

Tamoxifen appears to reduce the risk of cardiovascular disease and osteoporosis, but in a small percentage of cases, may give rise to damage of eye tissues, blood clots, liver, lung and gastrointestinal abnormalities and cancers. However, a survey of studies involving women taking tamoxifen by Zeneca Pharmaceuticals found that no conclusions could be reached about these complications, because each study achieved different results.

Several participants said some studies indicate that tamoxifen-related endometrial cancer may be more aggressive than the kind that has been liked to the use of estrogen replacement therapy without progesterone. Usually, endometrial cancer can be treated with a hysterectomy, said Peter Schwartz, director of obstetrics and gynecology at Yale Univ. School of Medicine.

No Recommendation On Aspiration

ODAC member Paul Bunn, director of the Univ. of Colorado Cancer Center, said that since progesterone is given to reduce the risk of endometrial cancer in women taking estrogen replacement therapy, progesterone might also be beneficial for users of tamoxifen. NCI is considering this type of study.

An NCI advisory group last month endorsed the recommendation of the trial's safety monitoring committee to resume the trial on condition that participants who have not had a hysterectomy undergo annual endometrial aspiration to detect endometrial

cancer early (**The Cancer Letter**, May 13). ODAC, however, declined to make such a recommendation.

"We really don't have a good method of screening for endometrial cancer," said George Willbanks of the department of obstetrics and gynecology at Rush Presbyterian-St. Luke's Medical Center in Chicago, an invited speaker.

There are no data on how reliable aspiration—viewing the lining of the uterus through hysteroscopy—or biopsy are as detection and diagnostic methods for endometrial cancer, Willbanks said.

Trevor Powles, head of the breast unit at Royal Marsden NHS Trust, said a study at the hospital suggested that endometrial thickness as measured by ultrasound may be a reliable, though expensive, way to screen for abnormalities. If the uterine lining is thicker than 8 mm, he said, then further diagnostic testing may be called for.

NCI sent letters to 30,000 physicians and pharmacists warning of the new findings about endometrial cancer.

Weighing Benefits Vs. Risks

That the study is subjecting healthy individuals to drug treatment was a concern throughout the meeting. David Ahmann of Mayo Medical School and a consultant to the committee, brought the issue up repeatedly.

"Keep in mind that we're talking about giving this drug to normal human beings," he said.

This issue was raised during a public comment period at the beginning of the meeting. Breast cancer survivors and representatives of national advocacy groups, speaking emphatically and at times emotionally, took sides for and against resumption of the study.

"The potential risks far outweigh the proposed benefits to the women in this trial," said Nancy Evans of Breast Cancer Action, and a breast cancer survivor. She accused science and industry of "preying on our fears" to enroll women in the study. "We know there's no free lunch, but we'd like a better look at the price tag," she said.

Adriane Fugh-Berman of the National Women's Health Network commented that "tamoxifen is too dangerous to use in healthy women." Further, she said there is no evidence that taking tamoxifen for five years will confer a lifetime benefit.

Preventive measures involving diet and exercise should receive more attention, she said. The tamoxifen study "is the wrong trial to do," she said.

ODAC Chairman Charles Schiffer noted that, "A diet trial does not preclude this type of trial."

Among those urging that the study go forward were representatives of the American Cancer Society, CANACT, the Susan G. Komen Breast Cancer Foundation, and the American Medical Women's Association.

Tamoxifen is "the most promising preventive we have now for breast cancer," said Margaret Hart of the Y-Me National Breast Cancer Organization. "I personally believe if I had been given tamoxifen after my first cancer, I would not have had a second tumor."

ODAC consultant Craig Henderson of Mount Zion Medical Center in San Francisco said he was concerned about the drug's overuse once it received approval for general prescription use—for instance, administration to women with only one first-degree relative who has had breast cancer.

Leslie Ford, acting deputy director, NCI Div. of Cancer Prevention & Control, said any conclusions in the study would be issued as guidelines or recommendations, rather than public health pronouncements.

The study, directed by the National Surgical Adjuvant Breast & Bowel Project, has recruited 11,000 women of the 16,000 needed.

NCI stopped all NSABP trials April 4 as a result of fraud at St. Luc Hospital in Montreal. NCI said last week that accrual for the group's treatment trials could resume at about 100 of the group's 485 sites that have passed audits. The prevention study will resume once the consent form and endometrial cancer screening recommendations are revised.

Capitol Notes

House Appropriators Allocate $11.3 B To NIH, $2.1B To NCI

The House Labor, HHS, Education Appropriations Subcommittee this week allocated $11.322 billion to NIH for fiscal year 1995.

The amount represents a $384.3 million increase of FY94 and $149.8 million below President Clinton's request.

NIH was a top priority of the new chairman of the subcommittee, Rep. Neal Smith (D-IA), sources said. Smith announced the subcommittee's rejection of the Administration's proposed one-year "pause" on reimbursement of indirect costs to institutions that received more than $10 million in federal grants in

FY94. The subcommittee has asked NIH to make other suggestions on indirect costs.

During the open mark-up session, Rep. John Porter (R-IL) tried to move the NIH increase of 3.5 percent up to 3.9 percent by moving funds from other programs to NIH. The NIH budget should be closer to the biomedical inflation rate of 4.1 percent, Porter said. The attempt was not successful, but Porter said he would appeal to the full House Appropriations Committee when it meets June 20.

The subcommittee allocated $2.138 billion to NCI, of which $219 million would be transfered to the Office of AIDS Research, where all AIDS funding is to be concentrated.

The bill language also:

- Broaden's the NIH director's 1 percent transfer authority so that it can be used for non-emergency purposes, subject to Congressional approval.
- Identifies $20 million for extramural facility construction, to be competitively awarded.
- Blocks automatic taps on NCI funding for two cancer studies and an automatic tap on facilities funding for primate centers.

The subcommittee's report language:

- Identifies $8.5 million for the NIH director's discretionary fund.
- Requests that NIH conduct an outside evaluation of the extramural grant program comparable to the intramural study that was completed last April.

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Reimbursement for the care of patients involved in investigational treatments was included in the three leading bills on health care reform.

The provision is contained in the bills passed by the Senate Labor and Human Resources Committee, the House Ways and Means Committee and the Senate Finance Committee. It is also included in the President's bill and several other health care reform proposals (**The Cancer Letter**, Feb. 25).

Another item of interest to cancer advocacy groups, creation of a trust fund that would finance biomedical research through a surcharge on heath insurance premiums, appears in the bills passed by the Senate committees on finance and health and human resources.

At this writing, the House Ways and Means Committee bill makes no provision for the trust fund. However, Rep. Bill Coyne (D-PA) is working on including the fund in a revised package.

The trust fund proposal is supported by 262 national groups. The American Society for Clinical Oncology was the most recent cancer related organization to express support for the proposal.

The acceptance of the two provisions makes it more likely that they will become part of the ultimate health care reform plan, regardless of whether Congress succeeds at enacting the package during this sessions.

"The cancer community, clearly, has put these issues on the table, and Congress is finally responding," Terry Lierman, executive director of the National Coalition for Cancer Research, said to **The Cancer Letter**.

Fewer than 40 legislative days remain for Congress to report a health care reform package.

The Senate Labor and Human Resources bill includes what several observers described as the most precise language on reimbursement for the care of patients involved in clinical trials.

Under the bill, the health plans "shall allow individuals, when medically appropriate, to participate in an investigational therapy, and shall cover the patient care" for individuals involved in qualifying trials.

The patients involved in trials would have to be receiving a "qualifying investigational treatment," defined as a treatment "the effectiveness of which has not been determined." The care would have to be administered "under clinical investigation as part of an approved clinical trial."

The health plan would not cover the costs of the investigational agent or device as well as the cost of managing the research.

The House Ways and Means Committee bill is expected to include similar language.

NCI Audit Finds "Low Quality" Research At Calif. Foundation

NCI auditors found "low overall quality" of clinical research submitted to the National Surgical Breast & Bowel Project by the Memorial Cancer Research Foundation of Southern California.

However, the audit found that the intellectual damage from the foundation's submissions to the B-06 study amounted to one patient.

The auditors examined the files of 28 patients, finding that seven of them were ineligible for the trial. Of the seven, five were determined ineligible by NSABP, one was not analyzed after having declined assigned therapy and one was followed by NSABP as an eligible patient.

As NCI auditors focused on the quality of data submitted by the foundation, they treated the quality of care as a tangential issue.

However, the issue of quality of care played a central role in the news story by reporter John Crewdson of the Chicago Tribune. In a story that appeared June 5, Crewdson cited the NCI audit and other sources to claim that at least four patients enrolled by the foundation in the NSABP study received inappropriate care.

Crewdson first broke the story of irregularities at the Los Angeles-based foundation after gaining access to the research files of the site's principal investigator, David Plotkin (**The Cancer Letter**, May 6).

The NCI audit report, a copy of which was obtained by **The Cancer Letter**, largely confirms Crewdson's earlier analysis of Plotkin's data. However, the report faults Plotkin for giving Crewdson access to research files. "The permission given by the principal investigator to allow access by a reporter to NSABP patient records represents a severe breach of patient confidentiality," the report said.

Lawrence Weinberg, a spokesman for Plotkin, declined to comment on the audit results. "At this point, Dr. Plotkin has not had any communications with NCI or NSABP and is awaiting the results of the audit he had requested in April," Weinberg said to **The Cancer Letter**.

Plotkin had given Crewdson access to his research files. He requested the NCI audit after learning that the Tribune was about to publish a news story based on the materials he provided.

The NCI auditors' conclusions follow:

- The overall conduct of clinical research at this site, relating to the process of patient recruitment (and therefore issues of eligibility, randomization, and obtaining informed consent), as well as the accuracy of patient data submission, was of low quality. There were serious problems related to the randomization procedure for NSABP protocol B-06, suggesting a lack both of understanding of respect for the scientific process by these physicians, as well as importance for procedural rigor in order to accurately examine the scientific hypothesis being tested.
- There was a high rate of patient ineligibility at this site. However most of these cases were not considered in the published analysis of B-06 by NSABP. Similarly, there was a high rate of refusal, with four patients declining out of eight otherwise eligible patients who were randomized to total mastectomy, and three patients declining out of 15 otherwise eligible segmental mastectomy patients. Again, the majority of these patients were not considered in the analysis by NSABP, since the analysis in the 1989 B-06 paper included only patients who accepted the treatment to which they were randomized. It appears that of the 29 patients entered from this site onto protocol B-06, either because of ineligibility, or because of patient refusal, only 17 patients were considered in the 1989 B-06 analysis. Of these analyzed patients, one patient was determined by NCI auditors to have been ineligible based on the surgical report. Additionally, three of these patients had randomization conducted following the date of surgery.
- There are significant concerns related to irregularities in the utilization of the randomization process for protocol B-06 at this site.
- There are also problems related to the obtaining of signed informed consent by some patients entered into NSABP B-06 from this site. While it was not possible during the audit to accurately evaluate whether verbal consent had been obtained in these cases, many written informed consents were obtained at a time (sometimes much delayed) following protocol entry.
- A final issue relates to whether the medical care of any patient was compromised by entry into this protocol. Clearly, this would not have been the case if only eligible patients were entered onto the protocol and if the data entered on these patients had been correct. However, two patients were ineligible for the study because of inappropriate pathology (multifocal lobular carcinoma in situ). These patients were entered into the protocol and randomized to receive segmental mastectomies, which would not have been the appropriate operation for this condition. One of these patients did recur approximately one year later in the same breast. [Another patient], although entered into the protocol and followed by NSABP as an eligible patient, had residual axillary metastatic disease after surgery, as described in the surgical report. Her later care included adjuvant chemotherapy and tamoxifen, which was appropriate. The patient with the incorrect ER/PR entry could conceivably have had a delay in administration of tamoxifen. In this case, however, it seems from the record that her primary oncologist was, in fact, aware of her correct tumor ER/PR status, and notes subsequently refer to her being on tamoxifen.

DCE Board Approves Concepts For Long Island Breast Study

Implementing a mandate from Congress, the NCI Div. of Cancer Etiology Board or Scientific Counselors approved a study of the relationship of environmental factors on Long Island to breast cancer.

At a meeting last week, the board unanimously approved three concepts to conduct the study. One of the concepts was a program announcement.

The study was mandated by the NIH reauthorization measure enacted last year.

To support the project, DCE proposed two interagency agreements involving the Environmental Protection Agency and Brookhaven National Laboratory.

EPA's Region 2, which includes New York, New Jersey and Puerto Rico, was already in the process of developing a geographic information system which includes much of the data NCI would need for the breast cancer study.

Brookhaven, located in Long Island, will assist in evaluating and linking data sets generated in the study.

NCI earmarked $100,000 for EPA over two years and $150,000 for Brookhaven over one year.

The program announcement carries no dollar commitment, since Congress did not allocate a specific sum for the study.

Resulting grants will be founded from the R01 pool.

Iris Obrams, chief of DCE's Environmental Programs Branch, and Marthana Hjortland, program director for biometry and epidemiology methodology, are program directors for the grants. Obrams and Gina Day are the NCI program staff for the two interagency agreements.

Harvey Simon, Marian Olson, and Bill Hansen are the EPA staff members; and Jerome Barancik and Caroline Kramer are the Brookhaven staff members.

The concept statement follows:

Geographic variation in cancer incidence and mortality rates has been well documented, both internationally and within the US. In particular, higher rates or breast cancer have been described for much of the northeastern and middle Atlantic parts of the US, as compared to other regions or the country.

At least some of this variation may be explained by differences in the population distribution or known breast cancer risk factors, especially menstrual and reproductive variables, and—possibly—dietary and nutritional factors.

However, there are concerns that environmental hazards may influence the geographic distribution or breast cancer. In particular, questions have been raised about potential hazards from concentrations of industrial chemicals, pesticides, and other manmade materials in the water, soil, and air.

Preliminary data have related some exposures to cancer occurrence.

There is, therefore, a growing public voice calling for valid scientific approaches to determine whether specific (point source) or general (cumulative) sources of environmental exposure to manmade materials show associations with cancer cases in location or time.

Apparent associations can then be tested in targeted research to evaluate the possibility validity and causality. In addition, methods are needed to visualize complex data in such a way as to simplify and make meaningful the distributions of exposures and cases of disease, to facilitate communication.

This program announcement encourages research into epidemiological and statistical approaches. For exploring the relationship between environmental exposures, relevant physical measurement data, and data on cancer cases and controls that occur in geographic proximity.

Interdisciplinary studies calling on the expertise of biostatisticians, epidemiologists, medical geographers, and computer specialists are encouraged.

Data would usually be captured in a form of a Geographic Information System, as well as individual data on cancer cases (related to location and time) and selected controls.

Research areas of interest include:

—Statistical approaches to assess the validity and significance of apparent associations in location-time between measured or recorded exposure data and incident cases of cancer compared with controls.

—Visualization techniques for communicating simultaneous exposure data and cancer incidence or mortality data for hypothesis generating and for purposes of conveying public health information.

The DCE board also gave concept approval for the following noncompetitive agreements:

—Evaluation of carcinogenic risks to humans, with the international Agency for Research on Cancer, five years, $610,000 first year.

—Exposure assessment program for occupational exposures, with the National Institute for Occupational Safety & Health, five years, $193,000 first year, total estimate $300,000.

—Cohort mortality study with a nested case control study of lung cancer and diesel exhaust among miners, with NIOSH, five years, $345.000 first year, estimated total $950,000.