11/15/91

THE CANCER LETTER

Vol. 17 No. 44
Nov. 15, 1991

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

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

Congress Passes HHS Appropriations, Includes $9 Billion For NIH, $575 Million Delayed Funding

Congress last week passed the Labor, HHS, Education Appropriations bill providing NIH with a $9 billion budget for fiscal year 1992, an increase of $733 million, or nearly 9 percent, over the FY91 level of $8.3 billion. The bill includes $1.989 billion for NCI, a $276 million increase, or 16 percent, over FY 1991, the largest single increase for

(Continued to page 2)

In Brief

Jane Henney, Former NCI Deputy Director, Named FDA Deputy Commissioner For Operations

JANE HENNEY, former NCI deputy director under **Vincent DeVita**, has been named deputy commissioner for operations of the Food & Drug Administration, FDA Commissioner **David Kessler** announced last week. Henney, vice chancellor for health programs and policy at Univ. of Kansas Medical Center, was deputy director of NCI from 1980 to 1985. The newly established position gives Henney responsibility for managing the agency's day to day activities. She will have line authority over all of FDA's major operational units, will supervise the daily activities carried out by the agency and will advise the commissioner on all issues affecting FDA's performance. "Jane Henney will be a tremendous asset to the agency," Kessler said. "Her impressive background in management and medical research, both in government and academia, make her uniquely suited to helping manage the FDA at this time of great change." She will take unpaid leave from KU Medical Center for her duty in Washington, which begins in January. . . . **HENNEY'S APPOINTMENT** is the latest in a series of appointments of new senior management positions established as part of an FDA reorganization plan announced by HHS Secretary **Louis Sullivan**. Four new deputy commissioners and one senior advisor to the commissioner will manage the major functions of the agency. Two of these positions have been filled. **Michael Taylor** is deputy commissioner for policy, and **Carol Scheman** is deputy commissioner for external affairs. Appointments to the remaining two senior management positions are expected to be announced soon. . . . **CORRECTIONS: The Cancer Letter's** Nov. 1 issue incorrectly stated the amount approved by Div. of Cancer Prevention & Control Board of Scientific Counselors for the Appalachia Leadership Initiative on Cancer. The board approved $1 million per year for five years, up to four awards, for a total of $5 milllion. Also in that issue, the date and volume number were incorrectly listed on the front page. The issue was Vol. 17, No. 42, Nov. 1, 1991, as noted on the inside pages.

$9 Billion NIH Budget Includes $575 Million Of Delayed Obligation

(Continued from page 1)

the Institute since 1976. Most of the increase, $223.4 million, may not be obligated until Sept. 30, 1992, the last day of the fiscal year.

The NIH appropriations includes $575 million of delayed obligation, spread among the institutes. The President's budget and the House had proposed an NIH budget of $8.82 billion with $400 million of delayed obligation. The Senate had proposed $8.98 billion with $606 million of delayed obligation.

Although the delayed obligation will not be expended until FY 1993, NIH considers the funding FY 1992 money. It is not yet clear how the delayed obligation will affect grants, contracts, or other mechanisms.

In addition, the conference agreement allows the NIH director to transfer up to $160 million of the NCI appropriations to other institutes for research "directly related to the prevention, treatment, or cure of cancer." Up to $15 million of the delayed obligation of $31 million for the National Institute on Aging also may be transferred to other institutes for Alzheimer's disease research.

The report of the House-Senate conference committee on the NCI budget emphasized concern about "the growing epidemic of breast and prostate cancer in the U.S." The report said, "The conferees urge, in the strongest way, that the National Cancer Institute make breast, prostate, ovarian, and cervical cancer its top priorities and treat these diseases with utmost urgency."

The conference report directed NCI to "place additional emphasis on prostate cancer research by establishing prostate cancer centers under the Specialized Programs of Research Excellence" (SPOREs), the new grant program begun a few months ago to establish nine centers for prostate, breast, and lung cancer. The conferees also agreed to a Senate amendment calling for establishment of a Matsunaga-Conte Prostate Cancer Research Center, named after the late Sen. Spark Matsunaga (D-HI) and Rep. Silvio Conte (R-MA).

The conference report said the NCI budget "includes sufficient funds to continue the program in proton beam therapy at the planned level," the program begun last year by Congressional mandate.

The report also said the conferees had appropriated sufficient funds to "achieve the goals outlined" in the House and Senate budget reports.

NCI Director Samuel Broder discussed some of the areas highlighted in those reports at the recent meeting of the National Cancer Advisory Board:

Areas emphasized in the House report:

--Proton beam: A $4 million add-on for the inital phase of construction and equipping of a proton beam facility.

--NCI was directed to use a portion of a $30 million increase to fund breast and ovarian cancer research, with the remainder to go to prostate cancer.

--Poverty and cancer, community activities conducted through the CCOPs, and a cancer vaccine initiative were specifically addressed.

--A $2 million increase for pediatric AIDS; a collaborative conference with the National Institute on Aging was directed as well as a demonstration study for payment methods for psychosocial activities related to cancer.

Areas the Senate emphasized:

--Women's health: an increase of $40 million was identified for breast, ovarian and cervical cancer; $30 million for breast and $10 million for ovarian and cervical cancer. Of the breast cancer earmark, $20 million is specifically for basic research to understand the cause and find a cure for breast cancer, while the other $10 million is to establish up to six SPOREs for breast cancer.

--NCI was directed to establish a SPORE for prostate cancer. In addition, the Senate places within the National Institute of Diabetes, Digestive & Kidney Diseases $3 million for a joint program of prostate research.

--CCOPs are to be supported at an increased level of $16.5 million, or about $4 million than they are currently funded.

The report also suggested establishing a center for retrovirus research, and specifically mentioned the

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.

expertise at Iowa State Univ. (Senate Labor, HHS, Education Appropriations Committee is chaired by Sen. Tom Harkin of Iowa).

--Senate also directed an expanded effort in pediatric AIDS.

--Information dissemination, the role of cancer centers, issues related to poverty and cancer, gene therapy, and international activities were also highlighted.

--Expanded emphasis on cancer associated with Native Americans was suggested.

--Longitudinal studies of DES-exposed women should be an NIH priority, the Senate said.

--Provided $3 million to the Neurology Institute for that institute and NCI to cooperate on expanded research on neurofibromatosis.

Staff in NCI's budget office this week were working out details of the Institute's plans for spending in FY 1992.

A complicating factor is the threatened Presidential veto of the budget bill over the so-called "gag rule" issue. The bill contains a provision that would allow health workers to discuss abortion with patients at federally funded clinics, which President Bush has opposed. Congressional insiders were hard-pressed this week to predict whether a veto would be overridden.

The bill includes the following appropriations for the institutes besides NCI:

National Heart, Lung & Blood Institute, $1.199 billion; National Institute of Dental Resaerch, $160.5 million; National Institute of Diabetes, Digestive & Kidney Diseases, $664 million; National Institute of Neurological Disorders & Stroke, $583 million; National Institute of Allergy & Infectious Diseases, $971 million; National Institute of General Medical Sciences, $818.9 million; National Institute of Child Health & Human Development, $524 million; National Eye Institute, $271 million; National Institute of Environmental Health Sciences, $253.9 million; National Institute on Aging, $387 million; National Institute of Arthritis & Musculoskeletal & Skin Diseases, $204.5 million; National Institute on Deafness & Other Communication Disorders, $149.8 million.

National Center for Research Resources, $315 million; National Center for Nursing Research, $45 million; National Center for Human Genome Research, $105 million; Fogarty International Center, $19.9 million; National Library of Medicine, $100 million; Office of NIH Director, $143 million (includes $7.5 million for extramural facilities construction and $18 million in discretionary funding, part of which is to be used to continue the James Shannon Director's Awards program); buildings and facilities, $103.8 million.

DCBDC To Contract For CEA Agents For Testing As Cancer Vaccines

Advisors to NCI's Div. of Cancer Biology, Diagnosis & Centers gave concept approval to a proposed new contract to fund the production of vaccine-like constructs or immunotherapeutic agents that may be tested in clinical trials with cancer patients.

Jeffrey Schlom, chief of the Laboratory of Tumor Immunology & Biology, told the division's Board of Scientific Counselors at its recent meeting that his laboratory has developed a possible cancer vaccine by placing the genes coding for carcinoembryonic antigen (CEA) into a vaccinia virus vector. When administered to patients as a therapeutic vaccine, this construct could provoke an enhanced immune response that would fight certain tumors.

Researchers are also working on inserting CEA genes into other vectors, such as baculovirus, and on developing a purified form of the antigen, he said.

Under the initiative, a master agreement with first-year funding of $300,000, the division will contract with companies to produce these agents in large quantities for use in clinical trials.

Following is the concept statement, approved unanimously by the board:

Development of clinical grade recombinant vaccinia carcinoembryonic antigen gene constructs and other recombinant vector CEA constructs to elicit specific active immunotherapy responses in carcinoma patients. Proposed master agreement announcement, $300,000 per year for five years; total $1.5 million. Two MAOs to be issued per year, estimated cost $150,000 each.

The objective of this solicitation is to make available to NCI clinical grade recombinant vaccinia virus CEA gene constructs and other recombinant CEA vector constructs for use in clinical protocols to elicit specific active immunotherapy responses in colorectal carcinoma, mammary carcinoma, and lung carcinoma patients. Under the proposed master agreement, NCI will create a pool of institutions or organizations capable of providing Good Laboratory Practices or Good Manufacturing Practices clinical grade reagents, analysis of reagents, and accompanying documentation for meeting FDA requirements. The organizations will demonstrate expertise in the development and validation of clinical grade vaccines in one or more specified areas.

The Laboratory of Tumor Immunology & Biology (LTIB) will identify those recombinant constructs for clinical grade development and will set priorities for scale up of reagents. Once institutions have demonstrated that they meet the required qualifications and a master agreement has been initiated, master agreement orders will be written describing each specific reagent to be produced and evaluated. Organizations holding master agreements that are capable of performing a given task will then be invited to submit protocols.

CEA is one of the most widely studied tumor associated antigens and is expressed by more than 90 percent of GI carcinomas, 50 percent of breast cancers, and 70 percent of adenocarcinomas of the lung. The LTIB has developed a recombinant CEA vaccinia construct (Int. J. Cancer 48:900-907,

1991). A 2.4kb cDNA CEA clone, containing the complete coding sequence, was isolated from a human colon tumor cell library and inserted into a vaccinia virus genome. The CEA gene was stably integrated into the vaccinia virus thymidine kinase gene. The recombinant was efficiently replicated upon serial passages in cell cultures and animals.

Rationale for the development of clinical grade recombinant CEA vaccinia constructs and other recombinant CEA vector constructs: a) CEA is widely expressed on human tumors, b) CEA is a poor immunogen, and co-presentation of CEA with a strong immunogen in a recombinant vaccinia construct may elicit a strong anti-CEA response, c) immunization of mice with rV-CEA constructs demonstrated protection against challenge with tumors expressing CEA, d) in mice containing established tumors, administration of rV-CEA led to reduction or elimination of tumor growth, e) humoral and cell mediated immune responses to CEA were demonstrated in mice and monkeys administered rV-CEA, f) no toxicity was observed in mice and monkeys receiving rV-CEA.

It is anticipated that initial protocols using these reagents will be phase 1 safety trials involving patients who failed conventional therapy. Subsequent studies will involve administration of rV-CEA following resection of primary tumors, in patients without a good prognosis. A criterion for entry will be immunocompetence; this will involve CD4/CD8 analyses, skin testings with a group of antigens, and analysis of T-cell proliferative responses.

The objective of establishing the master agreement is to solicit organizations to construct and produce clinical grade recombinant CEA vaccines that meet all FDA guidelines. This involves appropriate documentation and facilities that meet GLP and FDA GMP guidelines. Furthermore, Drug Master Files that meet FDA guidelines will have to be developed for each clinical grade reagent for inclusion into the Investigational New Drug Application. This involves safety, purity testing, and preclinical efficacy testing that meet FDA guidelines.

It is anticipated that 100 to 200 doses of each vaccine will be required for initial studies; further scale up will be required if the initial studies with that particular agent look promising. Recombinant CEA constructs will include pox virus vectors (vaccinia and avipox), baculovirus vectors, and other vectors as deemed necessary. Purified peptides and anti-ideotype MAbs that meet FDA specifications for clinical trials may also need to be produced. Protocols for the construction, production, and analysis of each clinical grade vaccine will be provided by NCI.

DCT Board Ok's DTP Recompetitions, PA Concepts In Radiation Research

The Board of Scientific Counselors of NCI's Div. of Cancer Treatment gave concept approval to the recompetition of five contract programs worth more than $23 million over three to five years, including four contract programs established by DCT's Developmental Therapeutics Program.

The board, at its recent meeting, also gave concept approval to two program announcements that would be released by DCT's Radiation Research Program. One would establish a working group to stimulate advances in digital mammography; research would be funded through NCI's new "interactive" R01 grants. The second PA would encourage development of nonionizing radiation technologies for breast cancer imaging. The board approved a third program announcement concept on AIDS related Kaposi's sarcoma, which is published in this week's issue of **AIDS update.**

Following are the concept statements:

Master Agreement Mechanism for Custom Products and Services. Recompetition of contracts held by Abbott Biotech Inc. and Synthecell. $2.8 million annually, five years; total $14 million. Under this proposal, BRMP will set up a system of Master Agreements to procure specialized products and services in support of its extramural and intramural research programs.

1. Chimeric Antibody Production: $600,000. Monoclonal antibodies of murine origin can be efficiently raised against a wide variety of antigens of great potential importance in cancer therapy and BRMP-sponsored research into HIV infections. There are three major obstacles hindering utilization of these substances in clinical research. First, technological problems and cost still limit the current availability of clinical-grade human monoclonal antibody. Second, the development of human antimouse antibodies restricts the clinical application of murine monoclonals. Third, murine antibodies mediate human immune responses variably, and often poorly.

Although human monoclonal antibodies would appear to be the best solution to the problems encountered with murine antibodies, human monoclonals are much more difficult to obtain than mouse antibodies, and are usually further limited by being of IgM class and having low affinity.

The Fc portion of the mouse immunoglobulin molecule is considered more antigenic than the Fab portion, and it is the Fc portion of the molecule which determines its effector function. Substitution of a human Fc portion for a mouse Fc portion in a mouse monoclonal antibody, therefore, would potentially reduce the undesirable antigenicity of a murine antibody and improve its capacity to mediate an antitumor response. A number of technological approaches can be taken to produce such hybrid molecules. Mouse-human chimeric monoclonal antibodies showing reasonable promise have already been produced, and some have entered clinical trials. "Humanized" monoclonals, which are potentially less immunogenic than chimeric monoclonal antibodies, have also been produced in limited quantities.

BRMP requires the capacity for producing chimeric mouse-human antibodies in quantities ranging from 100 mg through 1 g to 50 g, in both research and clinical grades, starting from a mouse hybridoma line producing the analogous murine antibody.

2. Custom Peptide and Protein Production: $300,000. Certain peptides and protein fragments are of great interest in cancer research. BRMP requires the ability to produce these entities from well-defined gene segments or protein sequences. In addition, the ability to produce custom hybrid proteins would allow creation of novel molecules with properties of significant research and therapeutic interest. For example, the combination of a toxin with a growth factor may allow unique manipulations of the target cells bearing growth factor receptors. Another example would be the coupling of two monoclonal antibodies to produce a bifunctional antibody. Such antibodies have been used to target cytotoxic T-cells to tumor targets. A third example would be the production of single-chain antigen binding molecules. Due to their small molecular weight, these molecules may improve cell targeting and delivery of antitumor and/or tumor imaging agents to vascularized tumors. The custom production of these new molecules would allow a wide range of new experiments and interventions. Rapid turnaround and flexibility to choose between a number of possible business and university sources argues strongly for a Master Agreement Order mechanism.

Analysis of Chemicals and Pharmaceutical Formulations. Recompetition of a contract held by Midwest Research Institute. $486,000 annually (50% cancer, 50% AIDS), three years; total $1.45 million. This is one of five contracts responsible for evaluating the identity and purity of bulk chemicals and formulated drug products. Reports of the analytical testing on bulk drugs and dosage forms are used as a basis for assessing the suitability of bulk drugs or finished dosage forms for use in pharmacokinetic and toxicological studies, formulation studies, or for clinical trials. These data are also supplied to the Food and Drug Administration (FDA) as part of the NCI's Investigational New Drug (IND) filings for new anticancer and anti-AIDS agents. Historical summaries of the data are used in preparing specifications for the various bulk pharmaceutical substances, for procurement actions, and for routine quality control of these materials.

Additionally, data on solubility and stability for the quantitation of drug in plasma. The data are also provided to other contract projects to facilitate formulation development and to aid in the analytical aspects of pharmacological and toxicological testing.

It is anticipated that the major thrust of project work will continue to be as outlined above. However, additional emphasis will be given to the expeditious development of analytical methods for the determination of structure and purity assessment of new agents.

The three contracts that were originally for the analytical assessment of cancer drugs are currently being recompeted with generic workscopes to serve both disease categories. Of the remaining two contracts (AIDS), one has been recompeted as a generic project for award in September 1991 for 5 years. The contract described herein will be competed as a generic requirement for a 3-year award to coincide with the expiration of the companion contract in 1996. At that point, we would plan to merge all of the contract analytical efforts into a single package for recompetition. A total of three awards would be anticipated.

Master Agreement for Large-Scale Isolation of Antitumor and Anti-AIDS Agents from Natural Sources. Recompetition of contracts held by Polysciences Inc. and Hauser Chemical Research, $1 million per year (50% cancer, 50% AIDS), five years; total $5 million. The mission of the Developmental Therapeutics Program (DTP) is the discovery and development of novel agents for the treatment of cancer and AIDS. The function of this project is to isolate and purify large quantities of active agents from plants and animals to meet program needs for the preclinical and clinical development of these agents. The isolation procedures used may be based on the initial laboratory-scale isolation procedures, but, in many instances, contractors must modify techniques or develop new strategies in adapting these processes to the bulk production of the agents. The contractors are required to follow good manufacturing practices (GMP); laboratories with GMP registration for bulk pharmaceutical production are highly desirable. The bulk drugs are analyzed under separate analytical contracts to ensure that they meet Investigational New Drug Application specifications for use in clinical trials.

The large-scale isolation projects for antitumor and anti-AIDS agents were originally maintained as separate contract packages, but are now being combined into a single project as reflected in this concept. The MA mechanism is being retained as the most appropriate mechanism for handling large-scale isolation projects.

New projects anticipated are the bulk extraction of needles of cultivars of Taxus species being harvested through an interagency agreement with the U.S. Department of Agriculture and a consortium of nurseries and several universities, and the isolation of camptothecin from Camptotheca acuminata. Camptothecin is required as a starting material for the synthesis of 9-aminocamptothecin, which is being developed towards clinical trials. Two other camptothecin analogs, topotecan and CPT-11, are being developed by pharmaceutical companies, and promising clinical results are likely to result in an escalating demand for camptothecin. Although, presently, adequate quantities of the agent are available from Chinese and Indian sources, a project for the cultivation of C. acuminata is being initiated in collaboration with USDA to serve as a back-up source.

With NCI anticancer and anti-HIV screens fully operational, the natural product isolation group of the DTP Laboratory of Drug Discovery Research and Development has discovered a number of novel active compounds, and it is anticipated that some of these will require isolation in large quantities for further development. It is important, therefore, to have sufficient capabilities in these agreements to accommodate an increased demand for isolation resources.

Since the last solicitation, Natural Products Branch staff have been contacted by a number of companies interested in participating in the MA large-scale isolation mechanism, including several from overseas. It is hoped that the pool of MA holders will be expanded to about five in the future. The estimated annual amount is based on past experience with taxol isolation projects in which the cost of processing a 10,000-pound bark collection has been approximately $200,000.

Services in Support of the Developmental Therapeutics Program. Recompetition of a contract held by Technical Resources Inc. $460,000 per year (50% cancer, 50% AIDS), five years; total $2.3 million. The Developmental Therapeutics Program (DTP) has, historically, utilized a support contract for assistance in selected tasks. With the initiation of the DTP AIDS drug discovery and development program in 1987, the contractor became increasingly involved in activities in support of programs in both disease categories. The contractor now has a significant role in the management of data from the DCT in vitro anticancer and anti-HIV screening programs through support to the activities of the network of drug development decision point committees.

The functions of these committees extend from an Acquisitions Input Committee for the synthetic and natural products acquisition program through the Biological Evaluation Committees for AIDS and Cancer, which evaluate, recommend, and prioritize active compounds from the respective screening programs; the Natural Products Program Committees, which review and track the data on natural product extracts and fractions; Operating Committees for AIDS and cancer drugs and for biological response modifiers; and the DCT Decision Network Committee. Over the course of the current contract, the direct involvement and interaction of the contractor's staff in these action point/decision point processes have become the predominant roles of the contractor and reflect more indepth program awareness and involvement than are normally expected of the typical broad support services contracts. It is estimated that at least 75 percent of the resources of the contract are being expended on a continual basis for this function, including technical documentation, editorial and word processing support, and related computerized data entry tasks. The remaining effort is apportioned, on an as-needed basis, to the planning and logistical management of DTP-sponsored conferences, seminars, and workshops, including the preparation of the proceedings, and to a variety of miscellaneous tasks such as the establishment and/or maintenance of files for the grants, contracts, and National Cooperative Drug Discovery Group Programs.

Since many of the files must remain in the Government facility, some of the clerical tasks are carried out onsite in the DTP offices. Provision is made for obtaining graphics, slides, and prints

on an emergency basis, primarily when needed to update data for presentation to the decision-making process of the drug discovery and development programs.

The number of cancer and AIDS decision-point committees now totals ten groups. Several of these groups meet weekly and some are structured to require a turnaround time of 48 hours for the preparation and distribution of ACTION summaries by the contractor. The remaining groups meet generally on a monthly schedule. In addition to the preparation of suitable minutes, support to these committees includes maintaining an updated computerized compound tracking system for four of the major committees. A separate Operating Committee was established in June 1990 for the review of biological response modifiers, and, as a part of the blending of interests of the DTP and the Biological Response Modifiers Program in the drug development process, this contractor is providing the technical documentation for this activity.

Other significant contributions have included provision of the services of a full-time senior programmer to the Information Technology Branch database working group for the implementation of the in vitro cancer and AIDS databases on the FCRDC VAX 8820. Considerable Technical Resources, Inc. contract staff hours and funds were devoted to this function and included the development of training materials for a VAX/VMS training course for selected NCI personnel and contractors.

During the latter part of 1990, the TRI group assisted in the implementation of a new DTP retrieval system to record and maintain information on the compounds under the purview of the Operating Committees. This system was developed in response to a request from DCT Director Bruce Chabner for a mechanism that provides, in easy retrieval form, a summary of all significant information on a compound. TRI staff are responsible for verifying the data input by NCI staff and for updating the ACTION items in the system following each Operating Committee meeting.

It is planned to recompete the contract as a resource for broad Program assistance. Experience gained over the most recent periods of the existing contract suggests that the greatest amount of effort should be apportioned to those tasks relating to the action/decision point committees and their role in the drug development process. As the frequency of these meetings results in significant usage of staff in the middle-to-high salary scale, some adjustments elsewhere in the effort would be necessary to compensate for the additional labor hours and associated costs. Under present conditions, a reduction in the effort for onsite clerical support would be manageable.

Biochemical Genetic Monitoring of Rodents. Recompetition of a contract held by Texas A & M Univ. $84,000 (75% cancer, 25% AIDS), five years; total $420,000. The Developmental Therapeutics Program Animal Program supplies inbred, first generation hybrid, and immune-compromised rodents to a large number of investigators in the U.S. and around the world. These investigators include NIH intramural users, NCI grantees, and other NCI divisions. A significant portion of the total production effort is directed toward immune-compromised mice for DTP therapeutic studies and human tumors. An animal program of this magnitude must include a quality-control component to identify potential histocompatibility and other problems in the production of inbred mouse strains. DTP uses two methods for assurance of histocompatibility with inbred mouse strains. Biochemical Genetic Monitoring (this procurement) involves the use of electrophoretic markers utilizing between seven and twelve designated loci for each strain. Major histocompatibility problems are identified within three days by this system. A second method (skin grafting) complements Biochemical Genetic Monitoring very well in that this method is much more sensitive, but problem identification may require up to 100 days. Yearly, this contract receives approximately three percent of the breeders from each foundation, pedigreed expansion, and production colony within our total program for quality assurance testing.

During the past five years, this contract identified a few strains of mice with minor compatibility problems, probably due to genetic drift. None of the problems caused any interruption in production. Since all animals from the foundation colonies and the pedigreed expansion colonies were identified by parent, we were able to go to the pedigree charts and eliminate any suspect family and/or line. This identification, by this contract, enabled us to make adjustments before a problem became significant.

Since several strains of mice within the DTP Animal Program are produced at more than one location, this contract confirms that from a genetic standpoint all mice of the same strain are genetically pure regardless of the contract location from which they were sent.

It is our intent to continue this effort for another five years. This is necessary to confirm or deny the genetic purity of the mouse strains produced by the Biological Testing Branch program. The new award will be effective Jan. 17, 1993.

Following are proposed program announcements approved in concept by the DCT board:

Digital mammography and related technologies. While a number of reports indicate that presently available digital techniques are largely experimental and result in the deterioration of spatial resolution and introduction of image distortions, it has been shown that the detectability of malignant microcalcification clusters with relatively early, primitive digital mammographic systems was equivalent to state of the art conventional mammographic studies despite lower resolution. Current literature indicates the need for further technologic advances (e.g., higher contrast and spatial resolution digital imaging), for further clinical evaluation of digital mammography, and for comparison to conventional studies before it can be accepted for clinical use. However, theoretical estimation presented at a recent NCI workshop by Hans Roehrig indicated a significant potential for improvement in image quality that may be achieved with digital mammography in the future.

The proposed research will stimulate the development and evaluation of new technologic advances in digital mammography (e.g., novel x-ray sensors and display devices, image receptors for cost effective detector systems, cost effective display technologies, new imaging techniques--e.g., dynamic, or "real time" imaging) in order to improve image quality and therefore breast cancer detection.

In addition to improved image quality, digital mammography may pave the way for the following possibilities: 1) image processing for improved tumor visualization, 2) automated computer aided diagnosis (detection and quantitation) to enhance performance of the human eye, and 3) effective image storage and transmission, including teleradiology as the means to bring prompt radiologic consultation from recognized experts in the field to community hospitals.

The proposed approach of this PA is comprehensive collaboration (with NCI assistance) between academic community and industry (e.g., design of receptor or display systems and other hardware/software development support) through a National Digital Mammography Working Group. The funding mechanism would be interactive R01s with five major components: 1) digital mammography, 2) image processing, 3) CAD, 4) teleradiology, and 5) preclinical and clinical technology evaluation.

Novel nonionizing radiation technologies for breast cancer imaging. Recent data indicate that novel technologies, such as conventional magnetic resonance imaging and ultrasound, may provide important diagnostic information in younger women and patients with radiodense breast when lesions need to be characterized (e.g., cystic vs. solid mass). Further clinical studies are required to define the comparative role and analyze the cost effectiveness of MRI and ultrasound in breast cancer characterization.

Dynamic contrast enhanced MRI has been shown to be a promising adjunctive diagnostic tool in the following clinical situations: 1) conventional mammography and physical examination fail to provide diagnosis, 2) the differentiation of dysplasia vs. cancer, and 3) small lesions.

Advanced MRI and ultrasound technologies appear to have an important potential for quantitative characterization of tumor biology. Novel ultrasound technologies, such as high field systems, modern pulse echo/color flow, and 2-D/3-D imaging, may improve image quality and provide improved anatomic and physiologic information. Novel MR techniques, such as magnetization transfer approach, diffusion/perfusion imaging, magnetic resonance spectroscopy and electron spin resonance, will provide additional quantitative biochemical, biophysical, and physiologic parameters for breast cancer characterization in order to facilitate treatment planning.

The goal of this proposal is to stimulate development and validation of novel technologies and imaging methods (free of ionizing radiation) for the detection and characterization of breast cancer.

Publisher, Law Firm Settle Suit Over Newsletter Photocopying

A newsletter publisher and a major Washington law firm recently settled a copyright infringement case the publisher brought to challenge repeated, cover to cover photocopying.

Washington Business Information Inc., Arlington, VA based publisher of 12 newsletters including the "Product Safety Letter," "Food & Drug Letter," "The GMP Letter," and "Washington Drug Letter," filed suit earlier this year in U.S. District Court in Alexandria, VA, against Collier, Shannon & Scott.

The settlement involved cessation of photocopying of WBII's weekly "Product Safety Letter," and a cash payment of an undisclosed amount, the publisher said in a press release.

WBII and the law firm also agreed to work together to have trade and professional groups including the American Bar Assn. and the American Newspaper Publishers Assn. develop policy statements to clarify photocopying questions. Exact terms of the settlement agreement were not disclosed.

WBII has filed several suits in which it claims that photocopying of newsletters hurts the newsletter publishing industry. In other cases, including with a Fortune 500 company, WBII has reached settlement of over $100,000.

WBII President David Swit said the settlement with Collier Shannon "vindicates our long-standing position that cover to cover photocopying of newsletters constitutes copyright infringement entitling us to significant statutory damages."

RFPs Available

Requests for proposals described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs, citing the RFP number, to the individual named, the Executive Plaza South room number shown, National Cancer Institute, Bethesda MD 20892. Proposals may be hand delivered to the Executive Plaza South Building, 6130 Executive Blvd., Rockville MD. RFP announcements from other agencies will include the complete mailing address at the end of each.

RFP NCI-CM-27727-72

Title: Preclinical toxicology and pharmacology of drugs developed for cancer, AIDS and AIDS related illnesses

Deadline: Jan. 3

NCI's Developmental Therapeutics Program is seeking organizations to carry out pharmacology and toxicology studies, the data from which must be suitable for filing with FDA as part of Investigational New Drug applications.Organizations must have the facilities and staff to carry out such studies and the management expertise to analyze and evaluate the data.

The contractor must perform all toxicology studies in accord with FDA's current Good Laboratory Practices Regulations. Organizations must also indicate their willingness to sign a confidentiality of information statement.

Multiple awards will be made under this solicitation and will be administered on a task managed basis. Task orders will be issued under the funded cost reimbursement level of effort contracts resulting from this solicitation. Assignments are estimated to involve two to four chemical agents annually per contract. Offerors are required to propose at both levels of effort (46,875 and 93,750 hours over a five year period).

The objectives of the task orders to be issued are 1) validation of analytical methodology to quantitate drug plasma levels in laboratory animals and to measure levels in rodents and dogs treated with the agent under study, 2) determination of bioavailability of drug after parenteral and/or oral administration, if efficacious drug levels can be attained in plasma in vivo, and if the drug crosses the blood-brain barrier (AIDS drugs), 3) assessment of acute and subacute toxicity in rodents and dogs including determination of a maximum tolerate dose, of dose limiting toxicities, schedule dependent toxicity, or the reversibility of adverse effects, and of a safe clinical starting dose, 4) the use of pharmacokinetic information to permit extrapolation of toxic effects across species by relating plasma drug levels to the time of appearance and severity of toxicity, and to establish the safety of potentially efficacious doses.

The principal investigator must have a doctoral degree in pharmacology/toxicology plus at least three years experience in directing, implementing, and evaluating drug toxicity studies in experimental animals.

The pathologist and analytical chemist must likewise have credentials that illustrate competence in serving as critical team members in the conduct of such studies.

The effort is currently being performed by Battelle Memorial

Institute, Southern Research Institute (two contracts), and Midwest Research Institute.
Contract Specialist: Jacqueline Ballard
RCB Executive Plaza South Rm 603
301/496-8620

Program Announcements

PA-92-06
Title: Small grants for lung, breast, & ovarian cancer clinical trials
Application Receipt Date: Jan. 23

NCI announces the availability of a program announcement to encourage the submission of grant applications for new pilot, phase 1 or phase 2 therapeutic clinical trials that take advantage of recent laboratory developments in the treatment of lung, breast, and ovarian cancers. New and experienced investigators in relevant fields may apply for small grants to test new treatment strategies or do pilot studies. The small grants research program provides maximum of $48,000 direct costs per year, for short term (up to two years) research projects. They are nonrenewable.

Clinical studies must involve human subjects and be designed to ultimately improve cancer treatment. New clinical trials dealing with treatment using drugs, biologics, radiation, or surgery, whether used as a single agent/modality or in combination, are appropriate. The clinical studies must be based on a strong rationale and preclinical data should support the underlying hypothesis.

Examples of categorical areas for R03 studies include: 1) biochemical modulation studies, 2) immunotherapy (monoclonal antibodies, cytotoxins, vaccines), 3) biological response modifiers in combination with chemotherapy, 4) studies of drug or hormone or radiation resistance and reversal, 5) therapies aimed at interfering with growth factor action, 6) therapies with novel mechanisms of action, and 7) innovative surgically based multimodality studies.

Earliest feasible start date for initial award will be September 1992. Nonprofit and for profit organizations, governments and their agencies, and occasionally individuals are eligible to apply. Applications may be from a single institution or may include arrangements with multiple institutions. Domestic and foreign institutions may apply.

Requests for a copy of the complete PA may be directed to Diane Bronzert, Cancer Therapy Evaluation Program, Div. of Cancer Treatment, NCI, Executive Plaza North Rm 734, Bethesda, MD 20892, phone 301/496-8866, fax 301/496-9384.

PA-92-14
Title: Model cancer control delivery systems
Deadline: None stated

NCI invites applications for studies to develop, implement, and evaluate effective organizational models for integrating cancer prevention and early detection services into existing prevention and primary care services being provided by health care system such as community and migrant health centers, public health clinics and public and university hospitals. Projects must focus on the organizational settings in which health care is delivered to low income, minority, and medically disadvantaged populations and how these settings can be adapted to enhance delivery of cancer prevention and control services. The primary objectives are:

--To test feasibility and effectiveness of modifying existing community and public health care delivery systems to increase delivery and utilization of counseling and early cancer detection screening regimens among persons who do not usually initiate contact with the health care system for purposes of receiving preventive care.

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

Special consideration must be given 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. Support of this program will be through the R01 and P01 funding mechanisms.

Public and private entities and units of state and local governments are eligible to apply. Collaboration between official health service delivery organizations and public health and medical research scientists experienced in cancer prevention and control is encouraged.

Requests for copies of the complete PA or other questions may be directed to Helen Meissner, NCI Div. of Cancer Prevention & Control, Executive Plaza North Rm 239G, 9000 Rockville Pike, Bethesda, MD 20892, phone 301/496-0273.

NCI Contract Awards

Title: Survey of compounds which have been tested for carcinogenic activity
Contractor: CCS Associates, Palo Alto, CA; $871,862.

Title: Analysis of chemicals and pharmaceutical formulations
Contractor: SRI International, Menlo Park, CA; $2,412,139.

Title: Synthesis of derivatives of polynuclear aromatic hydrocarbons
Contractor: SRI International, $1,214,146.

Title: Resources for procurement of human tissues from donors with an epidemiological profile
Contractor: Georgetown Univ., $359,270.

Title: Early detection research network
Contractor: Univ. of Pittsburgh, $743,490.

Title: Early detection research network tissue bank
Contractor: Univ. of Alabama (Birmingham), $863,890.

Title: Oncologic pain instructional and advisory treatment system, phase 2 (SBIR)
Contractor: Analysis & Simulation Inc., Buffalo, NY; $489,923.

Title: Software to aid in the meta-analysis of research studies, phase 2 (SBIR)
Contractor: LMP Associates Inc., Chevy Chase, MD; $378,392.

Title: Synthesis of congeners and prodrugs
Contractor: Research Foundation of State Univ. of New York, $1,071,791.

NCI, Aging Institute Conference

NCI, the National Institute on Aging and the American Cancer Society are sponsoring a conference Nov. 20-21 at the NIH Lister Hill Auditorium on "Perspectives on Ovarian Cancer in Older-Aged Women: Current Knowledge and Recommendations for Research." Purpose of the meeting is to identify and consolidate information that bears upon the early diagnosis and treatment of ovarian cancer in women aged 65 and older. Persons interested in attending may contact Janine Joyce, phone 301/468-6555.