THE CANCER LETTER

Vol. 13 No. 25

June 19, 1987

Subscription: $160 year North America, $175 year elsewhere

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DCT Gets Okay To Proceed With Human Cell Line Drug Screening, More Drug Discovery Groups

NCI's Developmental Therapeutics Program has received final (more or less) approval from the Div. of Cancer Treatment Board of Scientific Counselors to proceed with

(Continued to page 2)

In Brief

Koprowski, Niederhuber, Engstrom Chair DCE, DCT, DCPC BSCs; Roentgen Ray Officers Named

NEW CHAIRMEN of NCI Boards of Scientific Counselors include **Hilary Koprowski**, director of Wister Institute, who will head the Div. of Cancer Etiology BSC, replacing **Barry Pierce**; **John Niederhuber**, Johns Hopkins Univ., who replaces **Paul Calabresi** as chairman of the Div. of Cancer Treatment Board; and **Paul Engstrom**, Fox Chase Cancer Center, who replaces **Erwin Bettinghaus** as chairman of the Div. of Cancer Prevention & Control BSC. . . . **RAYMOND GAGLIARDI**, Pontiac, MI, is the new president of the American Roentgen Ray Society. Other officers are **Lee Rogers**, Northwestern, president elect; **Gerald Dodd**, M.D. Anderson, first vice president; **Rosalind Troupin**, Univ. of Pennsylvania, second VP; **Glen Hartman**, Mayo, secretary; and **Ronald Evens**, Washington Univ., treasurer. . . . **AARON JANOFF**, professor of pathology at State Univ. of New York (Stony Brook) has been awarded the 1987 Alton Ochsner Award relating smoking and health. The $15,000 prize and medal will be presented during the October meeting of the American College of Chest Physicians in Atlanta. . . . **LAWRENCE EINHORN**, Indiana Univ., will be the Bernard Lee Schwartz lecturer at the 11th annual Scripps Memorial Hospital Cancer Symposium in San Diego Oct. 19-21. His topic will be, "Testicular Cancer: A Model for a Curable Neoplasm" . . . . **BENNO SCHMIDT**, chairman of the Boards of Overseers & Managers of Memorial Sloan-Kettering Cancer Center and a principal architect of the National Cancer Program, received the MSK Medal for Outstanding Support of Biomedical Research at the center's annual academic convocation. **Willet Whitmore**, former chief of the Urology Service, received the Katharine Berkan Judd Award; **Gavril Pasternak** and **Kenneth Marians** received the Louise and Allston Boyer Young Investigator Awards; **Thomas Krenitsky**, Wellcome Research Laboratories, received the Aaron Bendich Award for outstanding former Sloan-Kettering students; and **Arnold Welch**, NIH scientist emeritus, received the C. Chester Stock Award.

DCT Board Gives Green Light To New Screening System, Cooperative Groups

(Continued from page 1)
implementation of its new in vitro, disease oriented human tumor cell line drug screening system, which will replace the compound oriented P388 in vivo prescreen everywhere except at the Institut Jules Bordet in Brussels. The new system also involves replacing the existing compound oriented NCI in vivo tumor panel screen with the new disease oriented in vivo testing program based on complementary use of human tumor cell lines.

DCT Director Bruce Chabner, his associate director for DTP, Michael Boyd, and their staffs have been developing the new system for more than three years.

The Board also gave concept approval to three new national cooperative drug development groups, in addition to the two previously approved, one of which is in operation and the other which had its applications reviewed by the National Cancer Advisory Board last month.

The first National Cooperative Drug Discovery Group initiative resulted in funding of four multidisciplinary, multi-institutional groups. Principal investigators for those groups are at Memorial-Sloan Kettering, Roswell Park Memorial Institute, Univ. of California (San Francisco) and Univ. of Florida (Gainsville).

Following the new policy which is emphasizing disease oriented drug development, RFAs for national cooperative drug development groups for lung and colon cancer were released last year, resulting in a number of applications which were reviewed in April. Those recommended for funding went to the NCAB last month, and their fate will be made known soon.

The newest round of RFAs in this program will be for National Drug Discovery Groups for Specific Disease Oriented Anticancer Treatment, with the specific tumor targets left up to the applying groups; National Drug Discovery Groups for General Mechanism of Action Based Anticancer Treatment; and National Cooperative Anticancer Model Development Groups.

Total estimated annual cost of each of the three categories of new groups is $2 million, which would support three or four groups in each category. Awards will be for five years.

The Board also gave concept approval for a new contract supported effort in development and implementation of mechanistically oriented antitumor drug screens, also at an extimated cost of $2 million a year for five years. A smaller program, a contract for development of an antifolate screen for drugs against opportunistic infections in patients with AIDS, at an estimated cost of $250,000 a year, also received concept approval.

DCT's advisors have been wary from the start about the drastic change in direction proposed by Boyd. The Board went along cautiously, with an ad hoc review committee organized to track preliminary efforts toward implementation and report back to the Board.

The committee met last December and again last month. David Goldman, a member of the committee and former Board member, reported the committee's recommendations.

"The committee strongly supports it," Goldman said, and he added that considering its potential in search for new agents to treat AIDS patients, the situation "is urgent." He emphasized, however, that "this is not just a screen. It is a research program and should be tied into basic research."

In describing the new system, Boyd said the projected scope accommodates initial in vitro screening of up to 10-20,000 substances, including both pure compounds and crude natural products, at multiple concentrations (up to five to seven dilutions) against each of up to 90-100 human tumor cell lines of appropriate types. In vitro followup testing and detailed in vitro evaluations could be made on from 100 to 200 leads per year identified from the primary in vitro screen.

Ultimate goals are to "identify a new generation of drug candidates for clinical testing against human cancers" and to "provide the basis for retrospective evaluation of the predictivity of the new disease oriented screening models for identification of new agents clinically active against human cancers."

The committee's recommendations, as drafted following the December meeting, were not substantially changed in May.

"Overall, members of the committee were impressed with the technical progress achieved since the previous review (September, 1985). It was considered that the project should proceed towards full implementation, having due regard to the advice and recommendations elaborated herein. In view of the severe financial constraints the

committee endorsed curtailment of the P388 in vivo screen at all centers except the Institut Jules Bordet, in order to support the costs of further development. It was also recommended that final implementation of the screening model be deferred until the full cell line panel had been selected, characterized and calibrated. The project, which still requires regular review, remains largely experimental at its present stage of development."

Among the committee's comments and recommendations were:

1. Cell line panel. "It was noted that a number of extensively passaged cell lines had been acquired, some of which possessed cytotoxic drug sensitivity profiles comparable to those of murine leukemia lines, thus failing to reflect the clinical sensitivities of the tumor in situ. Renewed efforts should be made to obtain established lines at much earlier passage numbers. An appropriate action might be to write an open letter to institution and departmental heads and to individual investigators stressing the pressing requirements for well characterized and documented cell lines. NCI should preserve the proprietary status of the contributors of cell lines by guaranteeing not to redistribute the lines to others without the written permission of the contributors. The efforts to establish cell lines from normal tissues is encouraged."

Calibrate With Wider Spectrum

2. Characterization. "It is clearly important to verify both the species and tissue of origin of the several cell lines and to test regularly for intraspecies cross contaminations in view of the substantial number of cell lines in use."

3. Calibration. "Investigators had standardized on the use of adriamycin for calibrating chemosensitivity. In general it was considered that a wider spectrum of agents should be used for calibrating chemosensitivities, including agents of known clinical activities for specific disease categories and agents possessing particular tissue selectivities."

4. Cell doubling times. "Concern was expressed that many of the cell lines possessed relatively short doubling times and that their prevalence might bias the screen towards the selection of antiproliferative agents. Further, a seven day assay had been adopted, regardless of cell doubling time. It was suggested that consideration be given to variations in inoculum size and assay duration, dependent upon the properties of individual cell lines. The question of density dependent cytotoxicity is also relevant to this issue.

"As in the previous review, members of the panel were concerned that the screen might not have the ability to detect agents which are active specifically against slow growing tumors. Antimicrotubular agents and glutacorticoids were mentioned as examples of compounds known to possess this property, as do nitrosoureas in large spheroids."

5. Role of human tumor colony forming assays. "These appeared no longer to be a component of the project. However, it was suggested that any correlations between HTCFA screening and that in established cell lines of the same type should be explored before any final decision on exclusion was made."

6. Metabolic activation. "Some preliminary studies using S-9 supernatants and microsomal activating systems were outlined. These reflected methodology already well established in the literature. It is understood that such methods may be adopted in selected cases where a given chemical structure might imply a role for metabolic intervention."

Possible Hiatus

7. Pilot scale screening. "Forty two cell lines had been adopted for the screening of 200 compounds since January 1986. The committee expressed strong reservations on the advisability of proceeding to full scale screening before the complete cell line panel had been selected, characterized and calibrated. Dr. Boyd warned that the work involved could take at least one year and, in view of the decision to discontinue the P388 prescreen, would lead to a hiatus in the presentation of compounds to the Decision Network Committee. Most members of the review committee were strongly of the opinion that DCT should not be pressured to maintain the present flow of compounds in the system. It was considered a major priority to perfect the new in vitro screening model before its routine implementation, thus engendering sensible confidence in its future predictions."

8. Human tumor xenograft models. "The conventional subcutaneous implant assay is simple to effect and can provide tumor volume measurements at several time points. However, doubts exist concerning the potential for cellular heterogeneity in the implant specimen. The tumors are generally encapsulated and highly vascularised, while the overall

assay is time consuming. The subrenal capsule technique gives agreeably rapid results, though at only a single assay point. The fibrin clot procedure may be a feasible alternative short term assay which overcomes the problem of implant heterogeneity, although the take rate is frequently low and variable. The microencapsulation assay seems versatile and relatively simple; the major drawback of this method relates to its physiological relevance. On balance, the review committee favored the use of the subcutaneous implant assay, though it recognized that further evaluation of all these models will continue."

9. Establishing new human lung tumor lines. " The review committee considered that the aims of this project were somewhat tangential to the overall screening program and accorded it a low priority."

10. Further development of the in vitro screening model. "Dr. Boyd pointed out that financial constraints within NCI prohibited the allocation of further funds to the screening experiment. Thus its ongoing development could be achieved only within existing program resources. Dr. Boyd proposed that curtailment of the P388 in vivo prescreen, at all centers except the Institut Jules Bordet, would provide the necessary financial resources to develop the in vitro screening model towards its ultimate implementation. The committee voted 15-1 in favor of that proposal."

DCT Board members agreed with most of the recommendations and added, in the motion to approve them, the suggestion by Robert Schimke that a permanent committee be established to advise DTP on issues related to implementation and to report back to the Board. Goldman said the ad hoc committee members agreed that a permanent advisory group is essential.

Isaiah Fidler, who served on the ad hoc committee, attended the Board meeting and offered a comment on what he said was "another layer of complexity. Do we want to develop new drugs to treat primary tumors, or to treat metastases? We do want to treat metastases." He said he endorsed Goldman's statement that the new system "is an experiment, not just a screening program."

Concept statements for the new drug discovery and model development groups and the related contract initiatives follow, with some editing for consolidation:

National Cooperative Drug Discovery Groups for specific disease oriented anticancer treatment. These will be cooperative agreements, awarded for five years, with an estimated total annual cost of $2 million which will support three to four groups.

The DTP drug discovery effort is being restructured to attain a desirable balance between rational approaches to the elucidation of new and improved anticancer treatments, and the traditional, more empiric, screening approaches. Fundamental studies and advances in biology, molecular biology, biochemistry, chemistry, pharmacology and immunology suggest that either approach can be mechanistically oriented, that is, aimed at inhibition of particular biological and biochemical actions leading to a broad spectrum of antitumor specificity; or alternatively, can be disease oriented, that is, aimed at selected and preferential action against particular tumor types.

For example, the in vitro and in vivo screening projects in operation at the Frederick Cancer Research Facility in conjunction with contract laboratories as well as DTP's planned biochemical screening program are relatively empiric in nature, although the former is specifically disease oriented while the latter is mechanistically oriented. A major step toward implementing interdigitated programs for the rational design, creation and preclinical evaluation of new anticancer therapies was achieved by establishment of the National Cooperative Drug Discovery Groups (NCDDG) program for assisting the concerned research communities to form multidisciplinary and multi-institutional groups whose goals are (1) the conceptualization and creation of new drugs and strategies to improve cancer treatment and curability; (2) the establishment of preclinical assays to examine the new drugs and strategies for both relevance to the rationale underlying their synthesis as well as to assessment of their potential for clinical efficacy; culminating in (3) the selection of new agents and strategies for development to the clinic.

The first four such groups, funded in FY 1984 and 1985, are mechanistically oriented in that they are directed to discovery of inhibitors of polyamine biosynthesis and function, inhibitors of oncogene expression, inhibition of DNA topoisomerases, and antireceptor monoclonal antibodies. Applications for disease oriented NCDDGs, specifically for discovery of lung and colon tumor treatments, have been recently reviewed.

It is proposed that cooperative agreements be established to form National Cooperative Drug Discovery Groups for treatment of specific human malignancies. Each group will be assembled by a principal investigator to form a multidisciplinary and multi-institutional consortium of those skills needed to successfully prosecute the conceptualization, development and preclinical investigation of new, rationally based treatments. The specific tumor type targets of the research will be selected by the applying group which will be expected to show the relationship between the proposed research and anticipated preferential efficacy against the chosen malignant disease.

Successfully competing groups will be funded via cooperative agreements, an assistance mechanism which differs from the more traditional grant in that the cooperative agreement permits a collaborative working relationship between extramural NCI staff and the award recipient. However, it should be emphasized that the applying group is expected to define its objectives in accord with its own interests and perceptions of exploitable targets for discovery of improved treatment. NCI participation would commence with award. A representative of NCI would then participate in the important deliberations of the group as a full member. This partnership would facilitate technology

transfer from government owned data bases and the use of appropriate contract resources to further enhance the efficiency and effectiveness of the group's effort.

The PI will be the conceptual focus of the group, and depending on the needs of the project, will extend invitations to appropriate scientists, regardless of their institutional affiliations, to participate as group members. The multi-institutional approach is envisioned because the existence of all of the highly creative talents in the required scientific disciplines will rarely be available in a single institution. Thus, the cooperative agreements may involve academic, nonprofit, and/or commercial/industrial institutions. Although activities related to the clinical introduction of a new agent (e.g., clinical formulation development, preclinical toxicology and performance of phase 1 clinical trials) are excluded from group activities, the collaborative effort among scientists working in the academic, reserch and commercial environments in close liaison with the government will enhance the efficiency of subsequent developmental tasks. Further, the preclinical information generated by such consortia of highly talented scientists will facilitate the enlightened conduct of early clinical trials.

National Cooperative Drug Discovery Groups for general mechanism of action based anticancer treatment. Five year cooperative agreements, estimated total cost $2 million a year, three to four awards.

Requirements and conditions stated above apply to these groups, except that the mission will be to establish National Cooperative Drug Discovery Groups to identify biological and biochemical sites of actions as targets for anticancer treatment discovery, and to design and create new and improved treatments whose antitumor specificity is attributable to exploitation of the specified targets. The biological or biochemical targets will be selected by each group.

National Cooperative Anticancer Model Development Groups. Five year cooperative agreements, estimated total annual cost $2 million, which would support three to four awards.

While the DTP screening and NCDDG programs are devoted to the discovery of new anticancer agents, ultimate clinical usefulness depends not only on the agents selected for preclinical evaluation, but also to a large extent, on the laboratory models used for the evaluation. Thus, there is a continuing need for the development of highly sophisticated preclinical assays which might discriminate for more effective clinical candidates. Also, it is important to recognize that there are creative biologists, molecular biologists, biochemists, immunologists, pathologists and other scientists whose primary interests may not relate to drug discovery per se and who may not be in a position to enlist the collaboration of appropriate medicinal and organic chemists to form viable drug discovery groups in the tradition of the NCDDG program. Nevertheless, these basic scientists are in a position, with appropriate NCI assistance and guidance, to translate fundamental findings to practical and predictive preclinical models for anticancer treatment discovery.

It is proposed that cooperative agreements be established to form National Cooperative Anticancer Model Development Groups (NCAMDG) to assist the most creative investigators in basic sciences to develop preclinical assays to be used in discovering and evaluating the anticancer potential of new drugs and strategies. Unlike the NCDDG program where the main emphasis is on the design of the agents to be tested, the main objective of the NCAMDG program is the elucidation of preclinical assays of greater potential clinical predictiveness than current screening systems. Areas of research will be broad and could include, for example, in vitro and in vivo models, biochemical models, metastatic models, immunological models, differentiation models, and radiomodulator models, etc. Agents to be used as tools to test hypothesized new models would be determined by the NCAMDG in collaboration with the appropriate NCI staff and would generally be supplied by DCT via its diverse acquisition and contract based screening programs.

A group could consist of a consortium of multi-disciplinary and/or multi-institutional laboratory programs from academic, nonprofit or commercial organizations whose research activities are clearly interrelated and aimed at a well defined objective. Alternatively, a group could consist of a single laboratory program working in collaboration with appropriate NCI extramural staff under the provisions of a cooperative agreement. In either case, the application for cooperative agreement will be assembled by the PI to include those skills needed to successfully develop new preclinical assays for the identification and preclinical therapy related evaluation of new anticancer treatments. Model development may be either mechanistically oriented or specific disease oriented.

Development and implementation of mechanistically oriented antitumor drug screens. Estimated total cost for the first year of five year contracts, $2 million. DTP anticipates that more than one contract will be awarded.

Recent advances in basic cancer research have made possible the identification of increasing numbers of targets for exploitation in anticancer drug development. Examples include oncogenes and their expression in malignant cell populations, tyrosine kinase, protein kinase C, phosphatidylinositol metabolism, and the various steps in the metastatic process such as laminan/receptor interactions and secretion for type 4 collagenase. In the specific case of small cell lung cancer, an example would be the autocrine growth factor bombesin. Identification of such targts makes feasible the development of specific mechanistically based antitumor drug screens. Such screens could be of great value when used in conjunction with the in vitro disease oriented human tumor cell line screening project currently under development at FCRF. This latter project is established as a primary drug screening model with a projected annual testing capacity of 10,000-20,000 compounds. A large number of synthetic compounds and natural products from the NCI repository and other sources is currently available for testing in addition to the rationally designed drugs developed under research grant support. Hence, decisions must be made on which compounds are to be screened and in what priority order. The potential of the human tumor cell screen for detection of compounds with selective cytotoxicity for particular tumor types could be significantly enhanced if relevant mechanistically oriented biochemical screens were employed for rationally selecting compounds for testing in the limited capacity primary screen.

Approach: Multiple biochemical targets with potential relevance to anticancer drug discovery are currently exploitable and employable. It is anticipated that multiple screens with varying capacities up to 10,000 compounds per year, depending upon the complexity of the test, will be employed. Considering the rapid advances in modern biological research, discovery of the target should be forthcoming. Accordingly, flexibility to add new screening targets with the option of retesting compounds which were negative in previous screening, will be maintained. Contracts for development and implementation of the individual screens will be awarded on a nationwide competitive basis.

Antifolate screen for drugs against opportunistic infections in patients with AIDS. One five year

contract, estimated annual cost $250,000.

The vast majority of patients suffering from AIDS eventually succumb to opportunistic infections by organisms which would not be able to gain a foothold clinically if the immune system were not compromised. For effective therapy, attention must therefore be directed at the therapeutic control of such opportunistic infections. Even a modest success against the more common infections conceivably may result in a dramatic prolongation of life, particularly if combined with clinically active antiviral drugs such as AZT.

The Developmental Therapeutics Program is instituting a major antiviral screening effort for anti-AIDS drug discovery and development. It is appropriate to couple this effort with an additional project to discover and develop in parallel potentially useful agents which can reduce the pathological impact of a variety of opportunistic organisms. There are several microorganisms, viral, bacterial, protozoal and yeast, which have been identified as pathogens in AIDS patients. The following represent some of the more common agents: pneumocystis carinii, toxoplasma spp., cryptosporidiosis spp., mycobacterium avium intracellularae, isospora belli, cryptococcus neoformans, candida spp., cytomegalovirus, herpes zoster and simplex, and Epstein-Barr virus.

The focus on an antifolate screen stems from the preclinical observations of Chabner et al that a candidate antitumor agent, trimetrexate (TMTX), an antifolate, had profound effects on the isolated dihydrofolate reductase from pneumocystis and toxoplasma. These studies have shown that two folate enzymes, dihydrofolate reductase and dihydropteroate synthetase,may provide a basis for a selective inhibitory effect against the organisms in a clinical environment. Subsequent clinical investigations utilizing TMTX to treat AIDS patients with pneumocystis carinii pneumona have shown promise. This intial lead is the basis for the current proposal in which folate analogs and analogs of p-amino-benzoic acid (PABA) would be evaluated for their potential therapeutic effects against any of the organisms which act as pathogens.

The use of isolated enzymes is suggested to permit a rapid assessment of possible differential effects on the various organisms responsible for clinical opportunistic infections. Schemes for isolation and purification of these enzymes could be provided by DCT. P. carinii, which is currently responsible for almost two thirds of the deaths in AIDS patients in the U.S., will clearly be a major focus for the proposed studies, and the technology exists for growing the organism in vivo in steroid treated rats and isolating its enzymes. Toxoplasm gondii, a second important AIDS related pathogen, can also be grown in vivo, is susceptible to antifolate therapy, and would be a second logical target for their screening effort.

It is recognized that it may be necessary to conduct developmental studies to establish the importance of various folate related enzyme systems. Many folate and PABA analogs are available to DTP in the NCI repository or from drug companies (Lederle, Merck and Warner-Lambert); repository compounds can be accessed through the computer based DIS. Any leads which are discovered would be subject to further development within the DTP preclinical AIDS drug discovery and development program.

Primary screening of HTLV-3/LAV (human AIDS virus). Recompetition of a contract now held by Southern Research Institute. Estimated total first year cost of the new, five year contract is $550,000.

This effort is currently being performed under a modification to a contract with the U.S. Army Medical Acquisition Activity and is being converted to a primary in vitro screen for the AIDS virus.

A limited number of preliminary studies involving in vitro assay development for primary and confirmatory testing for anti-HIV (AIDS virus) activity have been performed. Primary assays based on cell lysis and confirmatory assays have been developed, including dot-blot hybridization. Several cell culture systems have been developed, and small scale virus production has been used for inducing infection for drug screen assays.

Future plans: It is expected that this contract will evaluate approximately 5,000 compounds annually in an in vitro screen for potential therapeutic activity against HIV. In addition, this contract will perform in vivo testing with a limited number of actives from the in vitro screen. In vivo testing will be carried out in antymic mice.

Services in support of the Developmental Therapeutics Program. Recompetition of a contract held by Technical Resources Inc. Estimated first year cost of a five year award is $325,000.

DTP has historically relied on a support services contract for assistance in selected tasks. Originally these services were confined to support for the in vivo screening program. At the time in vivo screen was deemphasized, the contract was recast and competed as a program wide resource with a significantly broadened workscope. The contract is now designed to provide (1) services supporting the functions of decision point committees involved in the extramural drug evaluation and development processes; (2) planning and logistical management for DTP sponsored conferences, seminars and workshops, including preparation of proceedings; (3) maintenance of files for the grants, contracts and NCDDG programs; (4) special reports and other program related documents; (5) graphics, slides and prints on a rapid turnaround basis; and (6) a variety of miscellaneous tasks related to the planning and operational phases of the total DTP effort.

The contractor has been heavily involved in tasks supporting the development and implementation of the new approach to drug screening, and recently the effort has been accelerated to include assistance in the DTP AIDS drug discovery and development program. The contractor is now serving both facets of DTP in all areas of the workscope. Because of this major escalation of effort, additional funds from the AIDS appropriation are being added to the second year budget to meet the increased requirements (the AIDS supplement for FY 1987 was $75,000 out of a total cost of $248,000).

Future plans: The task requirements will be advertised essentially as presently documented, but at an increased level of labor and monies which is consistent with the involvement of the contractor in both the cancer and AIDS drug development efforts. An appropriate portion (50 percent) of the funds will be derived from the AIDS program resources.

It is anticipated that the neogiated level of the

The dollar estimates with each concept brought before the various boards of scientific counselors or other advisory groups are not intended to represent maximum or exact amounts which will be spent on those projects. They are intended as guides for board members to help in determining the value of the projects in relation to the resources available to the entire program or division. In the case of RFAs, the amounts cited are the maximum that will be set aside to fund those particular grants, the final amount depending on NCI's budget and program priorities. Responses should be based on workscope and description of goals and methods included in the RFPs (contracts) or RFAs (grants and cooperative agreements). Availability of the RFPs and RFAs will be announced when NCI is ready to release them.

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contract will be reached by as much as one year in advance of the original anniversary date, due to past and projected increases in usage of the services. Therefore early recompetition, as a small business set aside, is anticipated, for contract award during FY 1988.

Master agreements for the large scale isolation of antitumor agents from natural sources. This project was originally concept reviewed and approved by the DCT Board in 1984 at an annual amount of $200,000 for a three year period. Need for greatly increased isolation capacity will require the addition of an estimated $500,000 in FY 1988 and, since this exceeds the 50 percent increase allowable under the original concept approval, DCT asked the Board's approval for the increase, which was given.

The function of this project is to isolate and purify drugs from large quantities of plant or animal materials to meet NCI program needs for preclinical and clinical development.

One master agreement contract was awarded on a competitive basis to Polysciences Inc., in 1986, for a three year period, and annual solicitations have since been issued in order to obtain further qualified master agreement holders. The drug, taxol, has recently shown some promise in the treatment of melanoma in early clinical trials, and anticipated demand for large supplies (3-3.5 kg) to pursue clinical studies has resulted in a requisition for collection of 60,000 pounds of the source raw material, the bark of Taxus brevifolia, during the summer of 1987. The cost of the workup of 11,000 pounds of bark to produce taxol is approximately $250,000; thus, in order to permit the processing of 30,000 pounds of bark (yielding approximately 1.5 kg of taxol, sufficient to provide for 20 phase 2 trials of 30 patients each) during FY 1988, an additional $500,000 is required.

The Board also approved modification of DCT's contract with the Japanese Foundation for Cancer Research, originally established at a cost of $19,000 a year to serve as a focus for communication with Japanese industry and academia. The modification permits utilization of the contract as a mechanism to establish a bilateral exchange of postdoctoral fellows between the U.S. and Japan. Modeled after the successful NCI-EORTC Fellowship Program between the U.S. and Western Europe, this would fund up to 10 exchange fellowships throughout Japan or the U.S. for periods of two to three years. Half of the fellows' stipends would derive from this contract, with the other half contributed by the Japanese Foundation for Cancer Research. Revised annual cost to NCI is $169,000.

Since 1978, the contractor has operated a liaison office in Japan which gathers all new information developed throughout that country regarding experimental, preclinical and clinical cancer chemotherapy.

NCI CONTRACT AWARDS

Title: Tracing through credit bureaus to determine vital status and current address of patients treated for infertility
Contractor: Johns Holding Co., Decator, IL, $6,557

Title: Serum collection of voluntary participants, Breast Cancer Detection Demonstration Project
Contractor: Cancer Research Center, Columbia, MO, $145,056

Title: Provision of tissues and cells and conduct of routine tests in support of tumor cell biology studies
Contractor: Bionetics Research Inc., Rockville, MD, $3,783,479

Hope For Fatties: Avoirdupois May Not Increase Their Cancer Risk After All

For the overweight of the world, the news isn't always all bad. Assured by the experts that obesity causes or contributes to every ailment known to man, from flat feet to baldness, from impotence to breast cancer, they now can take some small measure of comfort in an unpublished NCI report summarizing findings to date from six grants awarded in 1985 for research into the relationship of obesity and cancer risk.

The results: For men, the relationship of obesity and cancer risk is so inconsistent that it does not even warrant further studies. For women, there may be a relationship to endometrial cancer and possibly to postmenopausal breast cancer, but that is about it.

Lest anyone be encouraged to head straight for the nearest pig-out eatery, an NCI staff member hastened to point out that "there are still many reasons why you should keep your weight down. It's just that cancer may not be one of them."

The report from a workshop held in April by the six grantees was presented to the Div. of Cancer Etiology Board of Scientific Counselors last week by Noel Weiss, a member of the Board. It follows:

"Six of the 21 applications responding to the (1985 RFA) were funded and will terminate on or before FY89. The grants consist of two case control studies of obesity and endometrial cancer; two prospective studies of the relationship between fat distribution and risk of the most frequently occurring cancers; and two endocrinologic studies which focus on either estrogen metabolism or the relationship between fat distribution and steroid hormone levels.

"(The April workshop in Palo Alto) was expanded to include investigators involved in other studies of obesity and cancer risk or expert in related areas, such as dietary assessment, the effects of physical activity, fat metabolism, or genetics.

"There were two purposes for the Palo Alto meeting: To review the ongoing studies with interdisciplinary problem solving and to explore the need for further stimulation of related research. Representatives from the staff and Council of the National Institute of Diabetes & Digestive & Kidney Diseases participated in planning and conduct of the workshop.

". . . In short, the studies have confirmed that obesity is less related to cancer risk than to several other chronic diseases, being more related to endometrial than to any other cancer; discovered that women with lower education have higher waist/hip ratios and that very obese women are slightly less responsive to questionnaires than others [ed. note: that figures--who likes to answer questions about their fatness?]; found that obese women produce more androstenedione than other women and that the derived estrone is metabolized through a more physiologically active pathway than occurs in other women; shown that women who smoke metabolize estrone differently, through the formation of compounds less physiologically active than women who don't smoke; and developed some evidence that women with android body fat distribution may have higher levels of testosterone and estradiol than women with gynoid fat distribution, who in turn may have higher levels of estrone. The data are too soft to draw any conclusions on a number of additional interesting points, some of which are unlikely to have been adequately explored before termination of the projects.

"Studies of prostate cancer lack consistency concerning the potential role of obesity. The reported study of male breast cancer found more association with body size than with body mass. Increased risk of cryptorchism and of testicular cancer in sons of obese women was reported in one study. However, in general, obesity does not appear to be relevant to cancer in men, or the relationship is found inconsistently. Stimulus focused on obesity as a cancer risk for men does not seem warranted at this time.

"Two interesting points concerned breast cancer in women. First, premenopausal women with cancer are thinner at diagnosis and have always been thinner than other women; however, women with postmenopausal breast cancer are more obese than other women. Thus, the relationship between body mass and breast cancer is complex. Concerning diet, alcohol appears to confer a greater risk than fat in the diet.

"Familial contributions to obesity and cancer can be disentangled if information is collected on both obesity and cancer in the relatives of cases and controls. Different mechanisms for interaction between obesity and genetic susceptibility in cancer etiology lead to different predictions about risks in relatives, which can be tested with appropriate data. . .

"NCI staff and advisors concluded that the ongoing studies are interesting and will provide useful information. Inconsistencies among studies of obesity and cancer risk for sites other than endometrium dampens enthusiasm for further stimulation. Reanalysis of previously collected data should be encouraged to determine if individuals with extreme values for body mass index are at different risk than individuals of average size."

NCI Pressing Search For New AD For Biological Carcinogensis

NCI executives are making an all out effort to stir up interest among highly qualified scientists in the position of associate director for biological carcinogenesis in the Div. of Cancer Etiology.

"I know we can't compete in salary, but I hope we can find someone with fire in his belly," Director Vincent DeVita said. DeVita and DCE Director Richard Adamson feel that the position is one of the best and potentially most exciting that NCI has to offer. Here's what the AD would do:

*Plan, direct and conduct a basic research program on the role of biological agents, genetic sequences, viral genes and combinations of viral and cellular genes is investigated.

*Direct and coordinate NCI's AIDS vaccine research and development efforts.

*Manage six intramural labs and an $80 million a year grant and contract program, with a total budget of $100 million and 175 full time scientists and staff members.

The official announcement for the position has a closing date of June 24. However, aplications will be accepted until the qualifications review board meets in mid-July. Send applications (form SF-171, available at all federal job information offices, CVs and bibliography, to Jean Craigue, NCI Personnel Management Branch, Bldg 31 Rm 3A31, Bethesda, MD 20892, phone 301/496-1771.

The Cancer Letter _Editor Jerry D. Boyd Associate Editor Patricia Williams

Published forty-eight times a year by The Cancer Letter, Inc., P.O. Box 2370, Reston, Virginia 22090. Also publisher of The Clinical Cancer Letter.