THE CANCER LETTER

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ARMAND HAMMER PANEL CHAIRMAN; DEVITA ANNOUNCES GREENWALD APPOINTMENT; ADAMSON TO BE DCCP DIRECTOR

Armand Hammer, chairman of Occidental Petroleum Co. and long time backer and confidante of Ronald Reagan, was appointed chairman of the President's Cancer Panel last week by his old friend. He replaces Joshua Lederberg, whose term had expired, and joins other Panel members Harold Amos and Bernard Fisher.

Cancer Program advocates who have longed for another Benno Schmidt (if not Schmidt himself) could not have been more delighted.

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In Brief

NCI CLAIMS "MAJOR FINDING" IN TREATMENT OF SOFT TISSUE SARCOMA WITH THREE MODALITIES; 93% SURVIVAL

NCI'S CLINICAL trial for treatment of soft tissue sarcoma has produced what the principal investigator, Steven Rosenberg, calls "a major finding" involving a "treatment strategy" which has doubled survival and avoided amputation in a majority of cases. Rosenberg, chief of the Div. of Cancer Treatment's Surgery Branch, told the DCT Board of Scientific Counselors last week that the study has produced disease free survival of 91 percent and overall survival of 93 percent by combining surgery, radiotherapy and adjuvant chemotherapy (adriamycin, cyclophosphamide and high dose methotrexate). This is the strategy Rosenberg recommends: Limb sparing surgery to achieve negative resection margins, followed by radiation and chemotherapy. If it is not possible to get negative resection margins, then amputation should be performed. Aggressive resection of pulmonary metastases should be performed when it occurs. Rosenberg said there were no local recurrences in 37 patients treated in that manner since 1975. (Rosenberg's preliminary report to the DCT Board last January was quoted in the February 1981 issue of ***The Clinical Cancer Letter***. A complete account of the latest report will appear in the October issue.) . . . . **HERBERT RAPP**, chief of the Laboratory of Immunobiology in NCI's Div. of Cancer Biology & Diagnosis, died Sept. 25 after a long illness. He was 58. Rapp was one of the major contributors to the development of immunology with his "creative, imaginative . . . classical work," DCBD Director Alan Rabson said. . . . **ABSTRACT DEADLINE** for the Third Conference on Human Tumor Cloning in Tucson Jan. 10-12 has been extended to Nov. 1. Contact Mary Humphrey, Univ. of Arizona Cancer Center, Tucson 85724. . . . **BREAST CANCER** Task Force has scheduled a meeting Oct. 28 on "Risk Factors in Breast Cancer: An Update with Emphasis on Interaction." The meeting will be held in the Bldg. 10 Amphitheater, National Naval Medical Center, in Bethesda, starting at 8:30 a.m.

GREENWALD TO START AT DRCCA TODAY, ADAMSON WILL BE NEW DCCP DIRECTOR

(Continued from page 1)

With Hammer, they have someone with many of the attributes displayed by Schmidt during his term as Panel chairman in the first five years of the National Cancer Program—a man with a strong interest in cancer research, who has a close personal relationship with the President, and who appears willing to use that connection to support the program anytime it may be necessary to do so.

Hammer, 83, is an M.D. (Columbia, 1921) who never practiced medicine and became one of the world's most successful international businessmen. He has made substantial contributions to cancer research.

"Due to the good fortune I have had in business," Hammer said in remarks to the National Cancer Advisory Board Monday, "I believe I may have done more to assist in my originally chosen field than if I had practiced medicine." He has supported the Eleanor Roosevelt Cancer Foundation, endowed the Armand Hammer Cancer and Biological Center at the Salk Institute, and the Julius and Armand Hammer Health Sciences Center at Columbia.

"I believe that in this decade we may be on the brink of major breakthroughs in our understanding, control and treatment of many cancers," Hammer said. "I am excited by much of the progress we have already seen and about the potential of some of the newer scientific areas of investigation in which we will be working in the coming years. Of course we have no guarantees, but I believe the field of research has never been brighter or more exciting."

Hammer said he believes "we should do more funding through the private sector with unrestricted grants which may help to propel us forward at a faster rate. I intend to devote part of my time to carrying this message to the private sector and I hope you will help me with this."

The President's Cancer Panel was created by the National Cancer Act of 1971. Its role is to advise the President on needs and problems of the Cancer Program and to make recommendations on the appointment of the NCI director.

During the Nixon and Ford Administrations, the Panel exercised considerable influence at the White House. The Carter Administration all but ignored the Panel, delaying appointment of a successor to Schmidt for two years and then paying absolutely no attention to him. Lederberg showed little inclination to pound on doors, and in fact did not attend most of the Panel meetings during the past year.

It will be difficult for the Reagan Administration to ignore the Panel now, if Hammer demands attention.

NCI Director Vincent DeVita announced several key staff appointments at Monday's NCAB meeting, including that of Peter Greenwald as director of the Div. of Resources, Centers & Community Activities.

Greenwald's appointment became known earlier when DRCCA Acting Director William Terry announced he was returning to his position as head of the Intramural Immunology Program (***The Cancer Letter***, Aug. 14). DeVita could not publicly acknowledge the appointment until it had been approved by HHS Secretary Richard Schweiker; that approval came through last week.

Greenwald, 44, has been director of the Div. of Epidemiology in the New York State Health Dept. He was scheduled to start today (Oct. 9) at NCI.

Greenwald received his M.D. degree from Upstate Medical Center, New York. He interned at Los Angeles County/USC; worked for two years in the Public Health Service with the Center for Disease Control; completed a medical residency in Boston City Hospital; received masters and doctorate degrees in public health from Harvard; and was an assistant in medicine at Peter Bent Brigham Hospital. He is certified in internal medicine and public health.

DeVita said Greenwald also would assume the editorship of the *Journal of NCI*, vacant since John Ziegler left last summer. Noting the heterogeneity of DRCCA, Greenwald told ***The Cancer Letter***, "that will help me keep up in all those fields."

Greenwald said the strengths in the division include the centers and community oncology programs. "There's a lot of opportunity to continue building on those strengths." The new initiatives the division plans to undertake, the Hospital Oncology Program and chemoprevention clinical trials, "will require a great deal of effort and recruiting new people," he said.

Another appointment by DeVita but which has not yet been cleared with Schweiker is that of the permanent director of the Div. of Cancer Cause & Prevention.

DeVita told the Board only that appointments had been made and he hoped to be able to announce them this week. ***The Cancer Letter*** learned that Richard Adamson, who has been acting director for the past year, is DeVita's choice.

Adamson had been chief of the Laboratory of Chemical Pharmacology in the Div. of Cancer Treatment's Developmental Therapeutics Program. He has had a strong interest in carcinogenesis, which is one reason why DeVita chose him as acting director. During his year in that job, Adamson carried out a number of organizational changes including the move of some labs to the Frederick Cancer Research Center and establishment of four new labs, with a DCCP budget lower than the previous year and with no additional positions.

DeVita told the Board of the appointment of Bar-

bara Bynum as director of the Div. of Extramural Activities, which has been announced previously (*The Cancer Letter,* July 31).

Another appointment announced by DeVita Monday is that of Peter Fischinger as NCI associate director with primary responsibility for overseeing FCRC. Fischinger has been involved in the Virus Cancer Program.

DeVita told the Board of the appointment of Bruce Chabner as acting director of the Div. of Cancer Treatment, an appointment made last June.

A key position still without even an acting appointment is that of NCI deputy director. According to sources, DeVita has made his selection; by press time this week, *The Cancer Letter* had been unable to learn who it is.

FDA OKAYS TOXICOLOGY PROTOCOL, INDs RELEASED; DRUG PROGRAM UNDER FIRE

NCI's Drug Development Program, on its way to becoming the next major target of hostile forces in Congress and elsewhere, picked up one victory this week when FDA Commissioner Arthur Hayes approved the controversial new toxicology protocol.

Hayes rejected the citizen's petition filed by Robert S.K. Young, FDA staff member who resigned as oncology group leader in protest over FDA's acceptance of the protocol.

The new protocol eliminates the requirement for preclinical toxicity tests in monkeys before a drug may be entered into phase 1 studies. Toxicity tests are still required in two species, mice and dogs, to determine safe starting doses in humans. The new protocol permits phase 1 studies to start without completion of histopathology, required to determine organ toxicity. Histopathology must be complete before phase 2 studies can start, however.

FDA had agreed to the new protocol more than a year ago. NCI had completed preclinical tests under the protocol on several drugs and submitted two investigational new drug applications when Hayes asked that they be held up until he reviewed the controversy. Those INDs are now released, and two more filed since also will be released shortly.

The new protocol reduces the cost of preclinical toxicity testing and may make it more feasible for institutions and industry to assume more of the burden of drug development.

The Drug Development Program including clinical trials, has been the subject of probes by the General Accounting Office and by Sen. Paula Hawkins' Subcommittee on Investigations & Oversight.

Two Washington Post reporters, Ted Gup and Jonathan Neumann, have been investigating the Cancer Program for the past year. They zeroed in on anticancer drug development in the last few months, and NCI Director Vincent DeVita believes they will emphasize its negative aspects.

DeVita told the National Cancer Advisory Board Monday that a five hour "exit interview" Gup and Neumann had with him recently left him with the perception that their stories would focus on toxicity and drug related deaths.

"To talk about drug related deaths and not talk about the reduction in mortality. . . is not a balanced view," DeVita said. "That's taking drug related deaths out of perspective."

DeVita has been using the figure of 45 percent as the present five year survival rate, a 12 percent increase over the last 10 years, based on the latest SEER data. Assuming there are 700,000 new cancer patients a year (excluding skin and in situ cervical cancer), that is an improvement of 84,000 lives a year over 1971.

DeVita expects even more irresponsible criticism from an impending "20/20" television program. Judging from the interview conducted by the program's staff with him, DeVita said they appeared critical of the disinclination of reputable physicians to accept unproven treatment.

The Drug Development Program was started in 1955 with a special appropriation of $5 million from Congress to NCI. It reached a peak of $46 million in 1976, and has leveled off at about $40 million a year since (those figures do not include cost of clinical trials).

The cost trend started downward when the number of compounds screened for antitumor activity was reduced from 40,000 a year to 15,000. The screening system was changed, from the L1210 leukemia and other transplanted tumors to a P388 leukemia prescreen and a panel of mouse tumors and human tumor xenografts. The in vitro cloned human tumor cell assay is presently being tested as an addition to the screening system.

The contribution of the Drug Development Program to the reduction in cancer mortality is difficult to measure, but there is little question that it has played a major role.

In the future, that contribution is likely to be enormous, as the increasingly sophisticated systems produce increasingly effective agents.

Of the 30 or more anticancer drugs commercially available, 10 were in development well before initiation of the NCI program. Six were alkylating agents, and two were thiopurines. These drugs included nitrogen mustard, methotrexate, triethylenemelamine, 6-mercaptopurine, busulfan, chlorambucil, triethyene thiophosphoramide, melphalan, actinomycin-D, and thioguanine.

Twelve drugs were developed under NCI sponsorship: mithramycin, the nitrosoureas BCNU and CCNU, dacarbazine, cytosine arabinoside, bleomycin, asparaginase, adriamycin, and cis-platinum II.

NCI and the pharmaceutical industry collaborated

on the clinical evaluation of vincristine, vinblastine, cyclophosphamide, 5-fluorouracil, procarbazine, and uracil mustard.

A host of new drugs has been entered into clinical trials since 1975, and some of them have produced exciting results as investigators manipulate dose, schedules and combinations. These include thymidine, AMSA, PALA, misonidazole, pyrazolo-imidazole, 3-deasauridine, levamisole, aminothiadiazole, hycanthone, L-alanosine, indicine-N-oxide, bruceantin, maytansine, pyrazofurin, and anguidine. Analogs include diazo-oxo-norleucine, dichloroallyl lawsone, PCNU, pentamethylmelamine, ICRF-187, rubidazone, chlorozotocin, and AD-32.

Budget reductions have not been accomplished painlessly, and the pinch caused by cutbacks this year will:

—Substantially reduce the number of synthetic compounds acquired for screening.

—Cut back sharply on contracts for fermentation products.

—Eliminate all contracts for discovery of new plant products.

The 1982 fiscal year budget for the Developmental Therapeutics Program (drug development takes up most of it) is almost identical to 1981 spending, at about $51 million. The reduction in purchasing power due to inflation has to be made up somewhere.

DTP Director John Driscoll presented the cutback proposals to the Div. of Cancer Treatment Board of Scientific Counselors last week:

Synthetics

Change proposed—Reduction of synthetic acquisitions from 13,500 to 10,000 compounds per year.

Reason for the change—Tightening the selection criterion by 25 percent has been judged by Ven Narayanan, chief of the Drug Synthesis & Chemistry Branch, to have a minimal negative impact on the identification of new active lead compounds.

Technical consequence—Thirty-five hundred compounds identified by computer assisted methods as marginal in terms of uniqueness of structure and potential for P388 activity will not be acquired and screened. While this reduction should have a minor impact on the number of synthetics entering the tumor panel (225 vs. 250), any additional reduction would undoubtedly be counter-productive.

Financial consequence—Minimal acquisition cost savings, but a reduction of almost $875,000 in biological testing would be realized.

Fermentation Products

Change proposed—Reprogram and reduce the lead discovery program supported by contract.

Reason for the change—The contract mechanism has not been a productive method for the discovery of new fermentation derived agents.

Technical consequence—DTP will rely upon worldwide surveillance to provide crystalline fermentation products which are P388 active in vivo. During 1980 and 1981, this mechanism provided 97 and 14 active materials, respectively, as gifts. The contract program provided 35 and three P388 actives during the same period.

	Cost (thousands)		
Contracts	**Current**	**Proposed**	**Savings**
Fermentation (3)	2,000	1,000	1,000
Biotransformation (2)	342	0	342
Umezawa	166	266	-100
FCRF	2,761	3,161	-400
Totals	**5,269**	**4,427**	**842**

Financial consequences—Approximately $842,000 from the fermentation product contract program will be saved. In addition, savings of $250,000 in NCI screening costs will be realized. (Most of the in vivo screening costs of the three large fermentation contracts are provided by the contractors under a cost sharing arrangement.) Total savings, $1,092,000.

Plant Products

Plan A, change proposed—Abolish the plant product lead discovery program supported by contract.

	Cost (thousands)		
Contracts	**Current**	**Proposed**	**Savings**
Collection	450	200	250
Extraction (small-scale)	101	0	101
Extraction (large-scale)	270	270	0
Fractionation (3)	444	0	444
Prescreen development	113	0	113
Literature surveillance	110	110	0
Totals	**1,488**	**580**	**908**

Reason for the change—The contract mechanism has not been a productive method for the discovery of new plant-derived anticancer agents.

Technical consequences—DTP will rely upon worldwide surveillance to continue to supply approximately 20 P388 active, crystalline plant products per year obtained as gifts. The contract program has usually produced an equal number of P388 active crystalline materials.

Financial consequences—Approximately $900,000 from the plant products contract program will be saved. In addition, savings of $1.1 million in screening costs will be observed. Total savings (Plan A), $2 million.

Driscoll presented an alternate "Plan B" for plant products which would reduce the savings, retain one fractionation contract to work on the best leads currently available, and fund collections by the U.S. Dept of Agriculture at a higher level. All other contracts would be eliminated.

The Board readily agreed to the changes in the synthetic and fermentation products activities, but split between Plans A and B for plant products.

Board member Sharon Murphy said she favored Plan A. "That will reduce the contract work, limit to some degree the number of acquisitions. I think we

should hold up temporarily the entrance of new materials, and test what we have coming through the new screening program."

Board member Sydney Salmon said the proposal "troubled" him. "I have the feeling that the Drug Development Program is one of the more effective DCT efforts. It has not been easy, but the product has been a series of useful drugs. I think the best compounds are those made by nature, not by chemists. Let's not throw out the baby with the bathwater."

Board Chairman Samuel Hellman asked Driscoll if he was "throwing out the baby."

"Certainly not," Driscoll said. "We're not deemphasizing natural products. We get a majority of our material from Dr. (John) Douros (chief of the Natural Products Branch) world wide travel, plus free acquisitions. We pay a high premium for less from the contractors."

Summarizing the Board's position, Hellman suggested that the primary difference between the two plans would be retention of the fractionation contract. When he called for a vote, six were cast for Plan A, four for Plan B.

"We'll split the difference," DCT Acting Director Bruce Chabner said.

The DCT Board gave concept approval to three new contract supported resource contracts in the Developmental Therapeutics Program with an estimated total of $650,000 in first year costs; existing DTP contracts to be recompeted with an estimated first year total of $7.7 million; and noncompetitive renewal of DTP contracts with $785,000 in first year costs.

The new projects approved were:

Synthesis of congeners and pro-drugs. First year cost, $400,000, three years. The staff narrative describing the project:

Objectives of this project are (a) to synthesize congeners of compounds with activities not quite up to the level of DN2 with a view to enhance their activities and breadth of spectrum, and (b) to design and synthesize "pro-drugs" and other compounds that possess elements of both congener and pro-drug.

This project involves the synthesis of congeners of active compounds, "pro-drugs" and other compounds that possess elements of both conger and "pro-drugs." The lead compounds will include active compounds of synthetic or natural origin where further progress through the Decision Network is hampered because of factors such as: the activity is not up to the DN2 level, poor aqueous solubility, or inadequate chemical stability. The objective is to synthesize new compounds related to the lead compounds but which are designed to mitigate the specific difficulties observed for the lead compound. Currently, there is no mechanism available to meet these objectives.

Task order for computer support. First year cost, $100,000, four years.

Master contracts will be awarded to a number of selected contractors. Under this arrangement, various development and maintenance tasks for the chemical/biological system can be requested, as the need arises.

A number of tasks have been planned by the Information Technology Branch and would be supported under such master contracts. Two examples are as follows:

1. In order to produce satisfactory output, chemical structures must first be converted by computer to vector maps, which are used in subsequent output. A program must be implemented to carry out this conversion on all connection tables that are new to the system.

2. A need has been expressed for a computer program that will track chemical agents as they proceed through the NCI linear array. This program must generate regular reports and also provide to Drug Evaluation Branch staff warnings when completion of linear array steps begins to fall behind schedule.

Both of these tasks are well defined and clearly circumscribed. It is expected that work statements can be quite easily prepared and used in the rapid award of appropriate tasks.

Histocompatibility quality control. First year cost, $150,000, three years.

This is an important new area of animal monitoring in DCT. A new initiative of $50,000 will monitor genetic contamination problems with inbred rodent strains so that contamination will be identified as quickly as possible after receiving animals from the NIH repository and prior to distribution to the production areas and the research laboratories. Problems with a few inbred lines have been identified recently, which emphasizes the importance of early resolution of these situations.

A second aspect of this new area involves central rederivation at FCRC ($50,000) and at the recompeted Charles River (87199) contract ($50,000). The central rederivation will have very tightly controlled checkpoints before distribution of the inbred lines to the general production areas. Testing will be accomplished biochemically under the workscope of the new initiative. It is anticipated that this testing will be accomplished very rapidly and with a high degree of sensitivity. The overall effort will be cost-effective considering that a relatively small number of testing will be needed at this level of production and that the repercussions of "genetic mistakes" can be terribly expensive in terms of compromised research.

The contracts being recompeted are:

Prime contractor performance of protocol toxicology studies. Present contractor is Battelle Columbus Laboratories. First year cost, $3,248,000, plus $1 million option to be used if required.

For ease in management, this contract is divided into four tasks. Task I is concerned with protocol studies of agents destined for INDA filing. Single dose and five daily doses are administered to mice and dogs to develop data that will permit selection of initial clinical doses and to establish the toxic potential of cytotoxic agents. Task II is any portion of the above mentioned protocol. For example, CBDCA (NSC 241240) required mouse lethality and toxicity testing to complete preclinical testing of this agent before filing an INDA. These data were obtained under Task II. Task III is organ-specific toxicity testing. Gastrointestinal and renal toxicity testing of various platinum analogues were accomplished under this task as was the cardiotoxicity testing of several adriamycin analogues. Task IV addresses itself to administrative management (day to day monitoring of subcontractors, development of the individual drug protocols as required by the Good Laboratory Practice (GLP) regulations, site visits to subcontractors for assessment of compliance with the GLP regulations) and data handling.

Under the recompeted contract, it is expected that eight to 10 Task I protocol studies will be carried out each year. It is fully anticipated that efforts will be directed toward the toxi-

cologic evaluation of biologic products coming from the Biological Response Modifiers Program. But until the agents for such testing are selected and protocols developed, it is impossible to project actual costs. Radiosensitizers and radioprotectors will be evaluated under this task although protocols for these agents differ x1 and x10 regimens using rats and dogs) from protocols for the cytotoxic agents. The best estimate for costing of these studies is $200,000 for the laboratory work and $89,541 for the administrative aspects. At this time it is unknown how many agents of either type will enter toxicology.

A modest effort will be directed toward the development of in vitro toxicologic screens. Since the final bottleneck to the introduction of new oncolytic drugs into Phase 1 clinical trials is the required toxicology, the time and cost of testing new agents could be greatly reduced by demonstrating to the Food & Drug Administration the validity of more rapid, less expensive in vitro/target organ tests that correlate with the large body of in vivo toxicologic data. Examples of areas that could be initially investigated include: (1) the correlation of in vitro cytotoxicities (ID_{50}'s) with murine in vivo lethalities (LD_{50}'s); (2) the predictability of renal explant cytotoxicities for in vivo nephrotoxicities; and (3) the correlation of in vitro cardiomyocyte toxicities to in vivo cardiotoxicities. Because of the many unknowns cited above, it is not possible at this time to project the funding that would be required for this effort.

Since the DCT program is dynamic and constantly changing, new program directives will be developed as new initiatives are required. Such new directives could encompass developing protocols for long term evaluation of chemotherapeutic agents used in adjuvant therapies, and would by necessity include testing for reproductive toxicology, mutagenesis, and carcinogenicity.

The $1 million optional money would be utilized for the study (Task I) of additional cytotoxic agents identified by the Drug Development Program. This funding would allow for protocol testing of up to four additional agents.

Screening and detailed evaluation of antitumor agents and combined chemotherapy and modality studies. Present contractor is A.D. Little. First year cost, $270,000 (reduced by the Board from the staff's estimate of $450,000), three years.

Chabner and some Board members objected to the broad scope of the proposal. Murphy's motion to approve but limit the workscope to analog comparison was modified by Hellman's suggestion to leave the workscope flexible but limit the money to $270,000.

Synthesis task order. Present contractors are Research Triangle Institute, SISA Inc., Starks Associates, SRI International, Southern Research Institute, Univ. of Alabama, Collaborative Research, Mid-America Cancer Center, Southern Foundation for Research & Education, and IITRI. First year total, $638,000, three years.

Objectives are the resynthesis of a wide variety of compounds in quantities necessary for anticancer screening, including: (1) presumptive actives, (2) a few panel compounds, (3) radiosensitizers and radioprotectors, (4) nucleosides, and (5) compounds reported in the worldwide literature.

The quick reaction work order contract mechanism provides for the resynthesis of a variety of organic and/or inorganic compounds that have been identified by the program as meriting development. They provide the mechanism to pursue leads uncovered by biological testing by means of the resynthesis of known compounds in quantities sufficient for confirmatory testing. For each work unit or task, three master concontractors are asked to compete.

To date, 300 compounds have been synthesized by the task order mechanism in response to a variety of program needs and requests. Through this mechanism we expect to synthesize approximately 250 compounds per year to serve a wide variety of requests emanating from several sources such as the Prescreen Committee, Analog Committees, Intramural Scientists, Analog Development Committee, Radiosensitizer/-Radioprotector Working Group, and Literature Monitoring.

New fermentation, antineoplastic drug acquisition, evaluation, development and screening. Present contractors are Bristol Labs, Warner-Lambert, and Upjohn. First year cost, $1 million (reduced from $2 million by the reduction in the program approved previously by the Board), three years.

This recompetition is for the three major fermentation contracts to obtain novel antineoplastic agents. A multitude of different organisms (actinomycetes, yeast, and bacteria) are evaluated for their ability to produce various compounds with varied biological activities. These compounds are isolated and evaluated in the NCI in vivo screens. The prescreens, media, environmental conditions, etc., are periodically changed to maximize the chance of producing and isolating new compounds of interest. In addition, varied isolation techniques to obtain different organisms are being used.

Large scale isolation of antitumor agents from natural sources. Present contractor is Polysciences. First year cost, $270,000 (under Plan A), three years.

The contractor will be required to supply NCI with highly purified compounds isolated from plant and marine animal sources. The major task will be to produce bulk drugs for clinical trials and for advanced developmental work including pharmaceutics and toxicology in quantities of several grams to several kilograms depending on the potency of the compounds and NCI needs. Each major assignment will require workup of from several hundred pounds up to 20,000 pounds of plant or animal material. Anticipated major projects will include isolations of indicine-N-oxide (in clinical trials), taxol (currently in toxicology), 4-betahydroxywithanolide E (passed DN2A), phyllanthoside (likely DN2A candidate) and baccharin and isobaccharin (potential DN2A candidates). There are several other pure compounds in tumor panel testing which have good potential for becoming DN2A candidates and which will require pilot plant scale isolation if they become preclinical candidates. Pilot plant assignments are regularly reviewed and are subject to change depnding on the priority needs of the DTP program for bulk drugs from plant or marine animal sources. In addition to preparing bulk drugs for clinical and advanced preclinical use, the contractor will also be required to isolate smaller quantities of compounds for tumor panel testing and to perform extractions and partial purification of leads assigned to chemists for isolation in those cases where large amounts of raw material need to be processed to get enough of the active fractions for final chemical isolation and identification of the active constituents.

Rodent production centers. Present contractors are Harlan Lab Supply, Charles River Breeding Labs, Microbiological Associates, Southern Animal Farms, and Simonsen Labs. First year cost, $1.6 million, three years.

These contracts have functioned to expand inbred strains from the relatively small numbers obtained from rederived lines at primary genetic centers into the very large numbers (now approximately 100,000 breeder animals) needed for first-generation hybrid production, e.g., B6D2F1, B6C3F1, and CD2F1. These contracts have collectively operated to improve the quality of production at this level and to become more cost efficient.

Through competitive processes, those contractors who can maintain quality production and remain cost efficient will be selected so as to continue the upgrading of the program.

Operation of animal diagnostic laboratory. Present contractor is the Univ. of Missouri. First year cost, $110,000, five years.

This contract has made critical contributions toward the upgrading of animal health quality accomplished by the animal production program in recent years. The contractor surveys representative animals from all of the animal production contracts and provides a complete health profile. Problem areas have been promptly identified, allowing sufficient time for corrective steps to be taken in animal production areas minimizing any disruption of the movement of inbred and first-generation hybrid strains of rodents to research laboratories. These efforts have been especially important in the development of the very large nude mouse production program.

This contract will continue to monitor for animal health purposes at present level of effort and additionally (through contract modification) will assimilate data for this and other contracts of this type through computer processing in order to provide a continuing over view of animal health status throughout the animal production and utilization program.

Frozen tumor bank. Present contractor is Mason Research Institute. First year cost, $235,000, five years.

This contract has performed effectively in expanding experimental animal and human tumors, checking them for viability, and distributing of tumors upon request. Distribution has been to DCT drug screening laboratories, with some distribution to qualified research investigators, both in the U.S. and overseas.

A significant contribution has been accomplished in cooperation with the viral serological contract (Microbiological Associates). Old tumors have been tested for viral pathogens with the finding that a large number were contaminated unacceptably with LCM (a human viral pathogen, MHV (a serious mouse pathogen), polyoma (affects tumor growth), and other viruses. Most of such tumors have been replaced with noncontaminated lines. A virus profile is now available upon request for all tumors distributed in the NCI bank.

Operation of an animal virological diagnostic laboratory. Present contractor is Microbiological Associates. First year cost, $350,000, five years.

This contract has monitored the viral health status of laboratory animals from all the animal production colonies and from the testing laboratories that are involved in the DCT research program. It has been utilized to identify those animal production colonies capable of meeting quality standards set by the Animal Genetics and Production Branch, DCT, and to eliminate those colonies that were found not to meet these standards.

This contract also monitors the experimental tumors maintained by the NCI tumor bank as well as those used in the DCT cancer research program. Through efforts of this contract, a number of tumors were found to be contaminated with LCM (viral pathogen which can produce severe human illness), MHV (a viral pathogen which can produce severe illness in laboratory mice), and polyoma. Contaminated tumors were discarded and replaced with noncontaminated tumors from the original source.

This contract also was the only source of ectromelia vaccine during the recent outbreak of that disease and routinely furnishes vaccine as needed for protective purposes.

The contract will continue to perform at level or expanded effort (contract is partially supported by NIEHS and has been expanded to accommodate their needs). As more sensitive methods are developed and proven reliable, they will be adapted through contract modification and/or recompetition.

Operation of an animal virus serological surveillance lab. Present contractor is Northrup Services. First year cost, $80,000, four years.

This contract has routinely monitored animals from genetic centers, rodent production centers, first-generation hybrid production centers, and testing laboratories for viral pathogens. Testing has been performed on a schedule submitted by the project officer. Testing has been performed promptly and reporting of results has been accomplished with minum turnaround time. Testing results have been utilized to continue upgrading animal production facilities and to provide testing laboratories with an assessment of animal health status in these facilities.

This contract will continue at level effort. The purpose of a second viral serological diagnostic contract is to assure that competitive balance is maintained in this field from both a cost and a technical viewpoint.

Primary genetic center for guinea pigs in biocontainment environment. Present contractor is Charles River. First year cost, $80,000, three years.

This contract produced the first known successful derivation of Strain 2 inbred guinea pigs. Contract has been modified to include the rederivation of inbred mice as directed by the project officer, and will represent a very important part of a coordinated central rederivation/histocompatibility testing effort which is designed to eliminate present concerns about the genetic integrity of a few inbred mouse lines.

Iso-antigenic typing of mouse strain. Present contractor is Northwestern Univ. First year cost, $65,000, three years.

This skin grafting contract has provided assurance that inbred lines are histocompatible with the NIH repository breeder animals, thus providing assurance that cancer research with inbred and first generation hybrid animals is comparable on a genetic basis. A few lines have been identified with histocompatibility problems and were eliminated through the efforts of this contract.

Early identification is critical to eliminating genetic contamination problems in inbred strains of rodents. The implications of these problems are at least as serious as those involving animal health. Consequently, the skin grafting contract will be continued at the present level, but an additional histocompatibility effort will be undertaken in conjunction with a centralized derivation effort in order to assure that inbred strains are histocompatibly sound prior to distribution to genetic centers. The skin grafting technique is effective to identify both genetic drift and contamination; it identifies 80 to 100 markers but requires 100 days for results. The new initiative emphasizing biochemical techniques requires five days for the results on 10 to 12 key markers which adequately monitor genetic contamination but not genetic drift.

Projects approved for noncompetitive renewal (subject to technical review) were:

Preclinical and clinical evaluation of anticancer agents, Institute of Cancer Research, $125,000 first year, three years; supportive services in virology, immunology, and tissue culture, Biotech Research Labs, $160,000 first year, three years; and an additional $500,000 a year to establish and operate a chemical information system.

This last contract, with Chemical Abstract Service, had already been approved and awarded, at an estimated cost of $826,000 in FY 1982. The cost has increased substantially in the last two years, up from $529,000 in 1980.

Driscoll told the Board that the Environmental Protection Agency has a computer operation similar to the one DTP requires, and has agreed to help NCI

develop the software needed for its own system. The cost will be about $500,000 a year for three years. Driscoll estimated that with an inhouse system, the cost would be one third to one half the current contract with Chemical Abstract Service.

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP, citing the RFP number. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs to the individual named, the Blair Building room number shown, National Cancer Institute, 8300 Colesville Rd., Silver Spring, Md. 20910. RFP announcements from other agencies reported here will include the complete mailing address at the end of each.

RFP NCI-CM-27514

Title: *Screening of compounds using human tumors in athymic mice*

Deadline: *Approximately Nov. 30*

This contract will involve: 1) maintaining and operating a small colony of athymic mice; 2) maintaining a limited frozen tumor bank to provide back-up for tumor lines; and 3) conducting the testing of compounds by means of a panel of in vivo transplantable tumor test systems.

To be considered for award, respondents must meet the following qualifications: 1. Experience in conducting in vivo screening programs; 2. Understanding of the project's workscope; 3. Previous experience and current ability to house healthy athymic mice in sufficient quantities to carry out the project; and 4. Facilities which include an existing barrier for housing animals. This animal facility shall include, as a minimum, an absolute air filtration system, mechanical cage washing machines, auxillary power sources, autoclaves (steam sterilizers) with sufficient capacity for handling large volumes of caging equipment and animal feed and bedding.

Other facilities required are for the conduct of studies of human tumor xenografts in athymic mice, tumor transplantation, drug preparation and administration, conduct of biological characterization studies, and the operation of limited human tumor banks.

It is anticipated that one award will be made as a result of this RFP. It is also anticipated that award will be for a three year level funded period of performance.

Contract Specialist: Charles Lerner
RCB, Blair Bldg. Rm. 228
301-427-8737

RFP N01-CP-15786-59

Title: *Synthesis of kilogram amounts of retinoids for chemoprevention and toxicity studies*

Deadline: *Dec. 18*

The basic objective of this project is the synthesis of new retinoids, to be specified by NCI, at the one kilogram level, which will be used in studies on chemoprevention, toxicology and pharmacology. The contractor shall provide the required retinoids in a high state of purity, package them in sealed 100 gram containers (under inert gas), and send them as requested by NCI to laboratories throughout this country and abroad which are performing the long-term animal studies.

The specific retinoids to be synthesized will be determined by NCI. However, it may be assumed that retinoids of the following general types may be required under this contract:

1) Ring modifications of all-trans-retinoic acid; 2) Polar terminus modification sof all-trans-retinoic acid; 3) Polyene chain modifications of retinoic acid; 4) Polyene chain and polar terminus derivatives of retinoic acid.

In addition, as other new retinoids are synthesized and evaluated, they shall be considered for synthesis at the kilogram level under this contract. It is anticipated that a greater variety of retinoid structures will be considered for kilogram synthesis in the future. A three year effort is anticipated in the effective pursuit of this project.

Contract Specialist: J. Roland Castle
RCB, Blair Bldg. Rm. 2A07
301-427-8764

NCI CONTRACT AWARDS

Title: Resource bank and distribution center for cell lines useful in research in tumor immunology

Contractor: American Type Culture Collection, $1,098,149.

Title: Collection, storage and quality assurance and distribution of biological response modifiers –Task B

Contractor: Litton Bionetics, $573,177.

Title: Human tumor cell line bank for diagnostic studies

Contractor: American Type Culture Collection, $742,881.

Title: NCI budget formulation and fiscal projection model

Contractor: JRB Associates, $251,000.

The Cancer Letter _Editor Jerry D. Boyd

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