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OMB Restrictions On Reprogramming Threatens Grants Of Three Centers, Possible Restorations

Restrictions imposed by the White House on reprogramming appropriated funds is threatening to cut off NCI support for at least three cancer centers and to end any possibility that some cuts in other center core grants may be restored.

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In Brief

Indiana U. Planning "World Class" Cancer Center; UCLA Names Two New Cancer Control Directors

INDIANA UNIV. School of Medicine announced plans last week for what it called a "world class" cancer center there. To be known as the Walther Oncology Center (after Joseph Walther, founder of Walther Medical Research Institute), the center will be located in the $34 million medical research and library building, construction of which will start this year. The Walther institute will provide $1 million a year for five years as core program support for the center. Walter Daly, dean of the medical school, will serve as interim director until a permanent director is named. An external scientific advisory group chaired by John Durant, president of Fox Chase Cancer Center, will help guide development of the center. . . . . **NEW CANCER** control directors of the UCLA Jonsson Comprehensive Cancer Center are Ellen Gritz, director, and Alfred Marcus, associate director. They succeed codirectors Lester Breslow and Helene Brown, who asked to be relieved of administrative duties. Brown will concentrate on community applications and information activities, Breslow on health services research . . . **CORRECTION:** Reference to what NCI Director Vincent DeVita called John Bailar's use of "buzz words" (**The Cancer Letter**, May 23) and "countless billions" was to the entire amount spent by NCI on cancer research, not just treatment research ("It's countless only if you can't count to 13," DeVita said). NCI's total appropriations since the National Cancer Act of 1971 has been about $13 billion, and the entire amount the institute has spent since it was established in 1938 is about $15 billion. . . . **WEST COAST** Cancer Foundation is recruiting a senior scientist/epidemiologist to develop and direct a state funded, statewide cancer reporting system for California. Salary range is $66-78,000. Send resume to WCCF, 50 Francisco St., #200, San Francisco 94133, or phone James Hochstadt, 415-981-4590.

Four Existing Centers Left Unfunded Unless More Money Becomes Available

(Continued from page 1)

Only six of the 10 cancer centers whose core grants were recompeted in the current, 1986, fiscal year are assured of funding--Jackson Laboratory, Albert Einsten, Univ. of Rochester, Dana-Farber, Johns Hopkins and Northern California Cancer Program. Those all had priority scores up to 178, when the money budgeted for cancer center support grants ran out.

Four others are over that score, and unless more money becomes available, will not be funded--Vermont Regional Cancer Center, Fels Research Institute, Ohio State Univ. Comprehensive Cancer Center, and Georgetown Univ. Vincent Lombardi Cancer Research Center.

One new center, at the Univ. of Utah, definitely is being funded. Another, at the Univ. of Kentucky, was approved but did not make the 178 payline. A center planning grant for a consortium of minority medical schools will be funded.

NCI Director Vincent DeVita told the National Cancer Advisory Board that a reprogramming request was being prepared which would fund three of the four unfunded renewals--Fels, Vermont and Ohio State. DeVita did not mention any figures at the open session of the NCAB meeting, but **The Cancer Letter** learned that the recommended budgets for those three would total somewhat under $4 million. The amount NCI is considering asking to be reprogrammed is $5.1 million. Presumably, the difference would be used to restore some of the cuts from recommended budgets in the noncompeting grants and possibly also the reductions now planned for the competing awards.

It appears that even if the reprogramming is approved, NCI does not plan to fund the Lombardi or Kentucky grants. The only hope now for those two centers for NCI support this year lies with the possibility that Congress will go along with the effort by Rep. Silvio Conte (R.-MA) to add $6 million to the 1986 supplemental appropriations bill for NCI, earmarked for cancer centers.

Conte succeeded in getting the $6 million into the supplemental appropriations bill approved by the House, but it was knocked out by the Senate. The issue now is in the hands of a House-Senate conference committee. At the moment, that conference has not been scheduled, and it could be well into the summer before it is held.

The Conte amendment clearly states that the peer review process should be used in awarding the $6 million to centers. With no other caveats, it seems that DeVita would have the flexibility to make additional awards based on priority scores as well as to restore some of the cuts from recommended levels.

Flexibility--the magic word to government managers.

DeVita has been increasingly critical of the process now being called "apportionment." That was the process decreed by the Office of Management & Budget last year which forbids NIH institutes from reprogramming their funds unless comparable changes are made within NIH so that the total amount allocated to a given program, NIH-wide, remains the same.

If NCI wants to reprogram $5.1 million from its grants pool (which is where the money for the centers probably would come from if the reprogramming is approved) and add it to centers, some other institute, or combination of institutes, would have to agree to take the same amount from centers and put it into grants. That didn't happen last year when NCI wanted to transfer $2-3 million from RO1s to clinical research, and it isn't likely to happen this year, unless OMB makes an exception, which it can do.

DeVita told the NCAB that he is proposing a return to the system of dealing directly with OMB in apportioning NCI's money. He said OMB imposed the new system as a means to get control of the grants budget. "It was basically an attempt to get NIH to stop proposing increasing numbers of competing grants each year which, in turn, increases the noncompeting base and makes the budget get out of control, in their view. They felt they were being toyed with by the way we were approaching Congress."

The argument that the new system gives more flexibility to the NIH director to move funds around, to meet new opportunities, is not convincing, DeVita said. "That is not the way NIH is really constructed. All the institutes are really quite different, and it's a very difficult process for us to sit down between institutes and divide resources. It is not so difficult for us to tackle common problems. If you lok at the AIDS situation, you find that with our own appropriations three institutes have done very well working

out the problems of diagnostic tests, cleaning up the blood supply, drug development, and so forth. Dividing up an appropriation or arguing whether we should have three extra slots in the centers program is quite a different story."

DeVita said NCI was able to move quickly and fund the $2.5 million, six center IL-2/LAK cell study only because he was able to reprogram funds within the cooperative groups. That avoided the reprogramming from one funding mechanism to another, which would run afoul of the OMB edict. Additional IL-2 clinical trials may be another story, however. Some of those studies may be done under contracts, and "we'll have to get permission from NIH and OMB to do this."

Instead of dealing with "14 other appropriations as one big pool," DeVita said "I would prefer to deal directly with OMB, go to them and say, here is how we would like to spend our money, and have them say, look, as long as you hit this target at the end of the year in terms of numbers of dollars and you don't commit us to any more than we have all agreed on, fine. I don't think they care much more than that. . . I think we can go to them and say, we will not commit ourselves for things in the out years beyond what we have said we would. But leave us alone in the meantime. We will move money all over the house. You are always negotiating in one pool and dollars are falling out. You use them during the year as they fall out and put them back in later in the year. In a big budget like ours, you can do a lot of things with just negotiated dollars that are coming in."

DeVita said he and NCAB Chairman David Korn had met with Barry Clendenin, chief of OMB's Health Branch. Clendenin "listened patiently to what we said and gave us some indication that what I just said is correct. They were not wedded to the concept of apportionment as much as they were having us present them a fair budget and a fair estimate of what we meant to do and then stick with it, which I would be inclined to do."

DeVita does not usually openly criticize policies coming from the White House. "I am saying it now in an open meeting, that although this is a policy of OMB and therefore of the Administration, it is a policy that I think is subject to some question. Research is moving too fast for us to have to go through that many steps to make decisions."

Salick Successful In Raising Money, Proceeds With Building FCC Network

The developing phenomenon of the for profit, free standing cancer center, one which offers multidisciplinary care on an outpatient basis, has generated growing interest among clinical oncologists and investors, as well as considerable concern among academicians and competitors.

The FCCs developed by or with the help of CDP Associates Inc. have evolved from radiotherapy facilities into multidisciplinary centers at locations around the country. Nearly all are affiliated with or closely allied to major hospitals. A few other independents have grown up with no hospital affiliation and in fact are hotly competitive with nearby community and university hospitals.

Then there is Salick Health Care Inc., which announced about 18 months ago (**The Cancer Letter**, Jan., 1985, and subsequent) ambitious plans to develop up to 20 centers, each surrounded by a network of participating community facilities, all financed by the traditional ways American business has available to it--basically, the stock market.

Salick struck its first cancer center deal with Cedars Sinai Hospital of Los Angeles, and has been operating the cancer program there since last July while building a new facility adjacent to the hospital which should be completed within a year.

Earlier this spring, Salick announced plans for its second "major comprehensive outpatient cancer care center network" covering five facilities in three South Florida counties. This network will consist of two major facilities in Miami (Parkway Hospital) and Ft. Lauderdale (Northridge Hospital) and three community cancer centers in Palmetto, Kendal and Palm Beach Gardens.

The Florida network is being developed by the joint venture Salick arranged earlier this year with American Medical International Inc. Salick and AMI agreed to develop at least three FCCs on a 50-50 basis, with Salick receiving a management fee, with costs and profits divided equally.

To finance development of its Los Angeles center and fund its share of the joint venture, Salick raised $18 million last year through a stock offering. This year, another $30 million was raised through sale of convertible bonds. The stock, sold over the counter, initially traded for $12.50 a share,

split three for two, and this week was selling for more than $17. The bonds are commanding a 20 percent premium.

Bernard Salick, the company's chairman and chief executive officer, developed his business originally as an operator of kidney dialysis centers in the Los Angeles area. Those centers are open seven days a week, 24 hours a day, and Salick is convinced that much of their success is due to the around the clock availability of the service. The company's free standing cancer centers will be operated on the same basis.

"Cancer patients can get sick at any hour of the day or night," Salick said in a recent discussion with **The Cancer Letter**. "If they need help in the middle of the night, they usually have to settle for someone at a hospital who doesn't know anything about cancer or chemotherapy and how to treat its side effects. We will always have someone available with the expertise. And if a patient finds it more convenient, for whatever reason, to get his chemotherapy or radiotherapy or whatever, at 3 a.m., that service will be available."

Salick centers will offer the entire range of services required by cancer patients--diagnostic imaging, laboratory, pharmacy, blood banking, chemotherapy, radiotherapy, psychosocial, rehabilitation, dietary, educational and outreach programs.

While one of Salick's selling points has been that all those services will be available under one roof, enhancing the convenience for patients, the Florida network will not have radiotherapy at either of the major centers. "We had a problem with the certificate of need," Salick said. Radiotherapy will be available on a contractual basis from existing radiation facilities.

Gerald Rosen, recruited by Salick from Memorial-Sloan Kettering as medical director of the company, will serve in that capacity over all the company's centers. A medical director will be hired for each of the major centers, with Rosen continuing as medical director at the Cedars Sinai center.

Salick and Rosen are in the process of recruiting oncologists, oncology nurses and oncology administrators for their existing and planned centers. "We've been talking with the top five people at some of the biggest cancer centers," Salick said.

They have also been talking with some of the NCI-recognized comprehensive cancer centers about managing their clinical operations, Salick said. Although the company has limited itself to outpatient facilities, "under certain circumstances we might agree to manage an inpatient program, but our major thrust will continue to be outpatient."

Other items discussed by Salick and Rosen include:

*Most of the company's centers will have affiliations with universities. Cedars works with UCLA, which Rosen said is "an excellent institution, the best I have ever worked with." No affiliation has been worked out yet in Miami.

*Physicians at the centers will be encouraged to do clinical research, through NCI's Community Clinical Oncology Program or other programs.

*The Cedars center may join in the upcoming round of CCOP recompetitions.

*Salick and Rosen are convinced the trend to more emphasis on outpatient treatment for cancer patients will continue. The average cost of treating a cancer patient is $30-35,000 a year, they said, 85 percent of which is generated by inpatients, and 53 percent of that in the last two months. "When that is converted to outpatient or home care, the savings are enormous," Salick said.

*Why should an institution turn over its outpatient cancer program to Salick? Consider the arrangement with Cedars: Salick will pay Cedars a guaranteed $1 million a year, plus 15 percent of the pretax profit. "We offer management expertise, capital, new equipment, the finest facilities, at no cost to the institution," Salick said.

*How can Salick make any money with that much coming off the top? The company projects that it will treat slightly fewer than three percent of the 27,000 new cancer patients diagnosed each year in Los Angeles County. "We will be profitable, in fact more than profitable, if we do that," Rosen said. Salick added that the profit margins in his dialysis centers have been 20-25 percent, and he expects the same from the cancer centers.

Cedars gave Salick its $2 million a year radiotherapy business, in return for the guarantee and percentage. The company is purchasing new equipment.

*What's in it for the local physicians? "Office space, free, which they can move into, or they can retain their own offices," Salick said. "We'll generate new patients for them. With our marketing program, the patient flow will increase. We can lower the

physician's overhead drastically. He bills and retains his fees. And the cost to the patient will be much cheaper. We aren't going to take away anyone's patients. What we are doing will make it easier, more pleasant and more profitable for local physicians to manage their patients, and it will be better for the patients."

DCT Board OKs Bladder Cancer RFA; Organ Systems Program Batting 1.000

The Organ Systems Program, in a crucial test of its ability to sell the boards of scientific counselors of NCI's program divisions on reserving funds for OSP generated concepts, is still batting 1.000.

The Div. of Cancer Treatment Board of Scientific Counselors last week approved unanimously a concept for pharmacokinetics of agents for bladder cancer intravesical chemotherapy. The concept, submitted by the OSP Bladder Cancer Working Group, was approved as an RFA (request for applications), which earmarks $600,000 a year to fund five grants.

The Div. of Cancer Prevention & Control BSC had previously approved an RFA for a $400,000 a year, five grant study of pain control in pancreatic cancer (**The Cancer Letter**, May 23). During the first year of the revised OSP, only one of the series of concepts generated by the working groups came through as an RFA; the others were program announcements, with no guarantee of funding. All were approved by the BSCs, but working group members expressed some bitterness that most of the research suggestions they had worked hard to develop had merely been thrown into the RO1 pot.

One reason for the emphasis last year on program announcements was that NCI staff had doubts about the fate awaiting RFA concepts at the hands of the division boards. So far, their fears have not been borne out.

The DCT board also gave concept approval to recompetition of three contracts for the Developmental Therapeutics Program, including the big, $2.4 million a year toxicology contract; and another for the Biological Response Modifiers Program for the collection, storage and distribution of BRMs.

The board also approved a one year extension of the phase 2 clinical trials of activated human leukocytes which it had approved last February. The extra time is for followup.

Following are synopsese of concept statements approved by the DCT board:

Pharmacokinetics of agents for bladder cancer intravesical chemotherapy. Five awards, three years, total cost estimated $600,000 per year.

Goals and major objectives:

A. Develop collaborative studies to systematically evaluate currently available and new investigational agents for topical intravesical therapy of superficial bladder cancer.

B. Establish a small network of investigators who have the capabilities, facilities and patient resources to conduct preclinical and phase 1 pharmacokinetic studies on patients with superficial bladder cancer.

C. Develop and validate models which can be used for testing various physical and physiological factors such as concentration, volume, dwell time, pH, drug distribution, absorption and depth of penetration.

D. Identify properties of selected representative drugs which can be used as reference standards for selecting future candidate drugs for study.

E. Provide information on acute toxicities, and pharmacologic characteristics (distribution, absorption, metabolism and elimination) of selected agents, for potential use in phase 2 studies.

Several drugs have been shown in small studies to have efficacy in the intravesical treatment of superficial bladder cancer. Until there is a sound scientific basis for detecting major advantages of one drug over another, there is little reason for setting up large clinical trials to choose among them. The pharmacokinetics of antitumor agents is a relatively recent area of research. At the clinical level, pharmacokinetic information has yet to become a routine tool. Tailoring chemotherapy to a specific disease in a specific patient is a very complex problem; therefore, pharmacokinetic data coupled with clinical observations, represents an area of research where major effort is needed.

Pharmacokinetic studies are needed to reduce the degree of empiricism related to intravesical chemotherapy. Important factors include determination of the appropriate volume in which to place the chemotherapeutic agent. Should a large volume be used to improve contact between the drug and the bladder surface? Should a higher concentration be used? What is the optimal pH for drug activity?

The effectiveness and toxicity of an intravesical drug may depend critically on depth of penetration. Does it enter only the superficial cells or make its way into the lamina propria, muscle superficial cells or systemic circulation? Measurements of blood levels indicate that the higher molecular weight compounds, such as adriamycin and mitomycin C, do not enter the systemic circulation in significant amounts after intravesical administration.

Transitional cell cancers are the most successful targets for chemotherapy in the spectrum of adult urological neoplasms, with the exception of germ cell tumors of the testes. Approximately 70 percent of patients with bladder cancer present with superficial lesions, which include both low and high grade papillary neoplasms and flat carcinoma in situ. Endoscopic surgery for these tumors is a highly useful and acceptable procedure since morbidity and mortality are low with essentially no associated loss in bodily functions. The risk for metastasis is less than 10 percent, but the risk of new tumor occurrences is about 50 percent. There is 10-20 percent risk of grade and/or stage progression. New occurrences are multiple and tend to occur more frequently with time. They may be tumors that arise from progressive neoplastic growth of regions of epithelial hyperplasias, atypia or carcinoma in situ. Or they might result from implantation of tumor cells on the urothelial surfaces

that are traumatized during local resection or fulguration. Heterogeneity among cells in pathologically similar in nature is indicated by differences among tumors in responsiveness to intravesical chemotherapy. Intravesical therapy has been used with varying degrees of success to prevent or delay recurrence and to treat the existing lesions. Major goals are to determine the optimal use of chemotherapy to increase survival, maintain a functioning bladder, and prevent the need for recurrent cystectomy.

Knowledge of pharmacokinetics has become important for the effective use of several classes of drugs; however, the approach of optimizing treatments in experimental and clinical situations by using such information is still in a developmental stage. Absorption, distribution, metabolism and elimination of anticancer agents display broad variability among different species, strains and individuals. This is due to a number of factors which influence drug kinetics; some factors pertain to the presence and growth of the tumor, some depend on the host, and others are related to the manner in which the drug is administered.

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Concept Review Figures Are Estimates Only; RFPs, RFAs Are Not Yet Available From NCI

The dollar estimates with each concept review brought before the various boards of scientific counselors are not intended to represent maximum or exact amounts which will be spent on those projects. They are intended only as guides for board members to help in determining the value of the projects in relation to resources available to the entire program or division. Responses should be bnased on the workscope and description of goals and methods included in the RFPs (contracts) and RFAs (grants and cooperative agreements). Availability of RFPs and RFAs will be announced when the Institute is ready to release them.

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Several studies indicate that the presence of a tumor affects drug disposition as a result of structural and functional changes induced by the tumor in the host. The presence of a tumor can change the metabolic capacity of the liver, impair kidney function, or produce anemia or toxic factors in the blood. Drug disposal by the body relates to the circadian rhythm; the same amount of drug given as a single dose or in split doses can result in different tissue levels of the agent and can produce different therapeutic and toxic effects. Drug kinetics determined after single doses may differ from those of long term administrations. Drug interaction can alter distribution and change the therapeutic or toxic effects of antitumor agents. The metabolism of a drug can lead to activation or inactivation, and some drug combinations can cause changes in the drug concentrations in target tissues without effecting a noticeable change in plasma levels. Some drugs affect the uptake of other compounds in tissues, thereby affecting cell permeability and drug entry into cells.

There is a need to determine the distribution of drugs in various host tissues in relation to the toxic effects. The pattern of drug accumulation varies in relation to the drug investigated. Usually, the tumor concentrates drugs to a very limited extent compared to other tissues, but other organs may be sites of selective drug accumulation. In some studies a greater vascularity of small metastases relative to that of the primary tumor provides the way for greater concentration at metastatic sites.

In order to be meaningful, drug distribution studies must be integrated by appropriate information on the mode of action of anticancer agents and on their intracellular determinants of activity.

Board member Alan Rosenthal asked if there are any agents which have been carefully evaluated in animal models or in vitro tests. Ian Tannock, a member of the Bladder Cancer Working Group who presented the concept, answered that "it is not easy to do in vitro, and animal models are being developed."

"I have a problem with this," Rosenthal said, "since you don't have an agent you can use with confidence based on preliminary studies."

"That's not so," Tannock responded. "The basis is that (with some agents) you can delay recurrence. It is not clear that you can prevent it."

"But there are no in vitro correlates," Rosenthal insisted.

"Maybe a clever guy writing a grant (in response to this RFA) would include an in vitro component," DCT Director Bruce Chabner said.

"I strongly support this," Board member Lawrence Einhorn said. "It is an important issue."

The board agreed, and the vote to approve was unanimous.

Performance of protocol toxicology studies. Recompetition of a contract presently held by Battelle Memorial Institute. Five years, estimated annual cost, $2.4 million.

Investigations focusing on the hazards of antineoplastic compounds to healthy organs in intact experimental animals are the final steps in the preclinical stages of new drug development. Such laboratory investigations comprise the primary responsibility of this contract. Toxicology studies designed to meet this responsibility involve four major objectives: determination and safety assessment of an initial dose for clinical trial; determination of primary organ systems adversely afrfected by drug administration; determination of the reversibility of the adverse effects; and determination of schedule-dependent toxicity.

Data generated from studies on each new drug and evaluated in light of potential human toxicity comprise a major portion of the information required by FDA for an investigational new drug application.

The direction of the preclinical toxicology studies has shifted from an undirectional course to two highly integrated paths. The first path continues to be the elucidation of the potential adverse effects of new anticancer agents. The second is the acquisition and use of pharmacokinetic information to reliably extrapolate toxic effects across species by relating plasma drug levels (peak and steady state) to the appearance and severity of toxicity. Integration of these two courses permits a more rational evaluation of the role of schedule dependence in efficacy of drug as well as in development of toxicity. In the main, this is achieved through the operation and management of a prime contract in which the qualitative and quantitative toxicological profiles of antitumor drugs and modalities are determined in experimental reduction animals. For management, the prime contract is divided into four definitive tasks. Task 1 is devoted to the complete preclinical toxicologic evaluation of cytotoxic agents, radiosensitizers, radioprotectors, etc. Standardized guidelines using mice, rats and dogs are followed to determine the initial dose for phase 1 clinical trials, to verify safety of the initial clinical dose and to elucidate specific target organ toxicity and its reversibility. Task 2 studies are concerned with limited evaluations of drugs. These studies are performed to complete the toxicity profile on compounds for which some toxicology data are available. Task 3 involves development and implementation of in vivo and in vitro tests to evaluate organ specific toxicity. The special studies carried out under this task yield important information leading to development of new, more mean-

ingful toxicity testing studies. Task 4 of the prime contract deals with the administration aspects of toxicity testing such as data handling, subcontractor monitoring as required by good laboratory practice regulations, and financial and program management.

"That's a ferocious amount of money," Board member Robert Goodman commented. "Isn't it conceivable that you could do this in house?"

"Impossible," answered Michael Boyd, director of the Developmental Therapeutics Program. "It's the same old problem, of space and people. That also would be inconsistent with NIH philosophy. The facilities we have here are for basic and clinical research.

"It seems to me the costs are based on the amount of things you push through the system," Rosenthal said. "If you have fewer compounds, it should not be at this level."

"You're absolutely right," Boyd said. "The problem is our inability to estimate how many we're going to have. This is a maximum estimate. The last two years, we've shortstopped contracts, phased them out early. This depends on changing needs."

"This amount is not exhorbitant," Chabner said. "There's no way we can take drugs to clinical trial without this."

The vote to approve was unanimous.

Collection, storage, quality assurance and distribution of biologic response modifiers. Recompetition of a contract held by Meloy Labs. Five years, estimated annual cost, $450,000.

BRMP has the responsibility for preclinical and early clinical evaluation and development of a wide variety of biological response modifiers with potential for cancer therapy. An important aspect of this responsibility is the procurement, quality assurance, control and distribution of various BRMs to qualified preclinical and clinical investigators. The purpose of this contract has been to provide effefctive management of these functions for BRMP. The contractor currently is responsible for receipt, dispensing, storage, distribution and inventory control of biologic agents. Quality assurance and control evaluation involves specific assays for sterility, pyrogenicity, endotoxin levels, general safety testing and preclinical studies related to safe dose and route of administration.

The contractor is responsible for processing, vialing, labeling, potency and purity testing of biologics obtained in bulk form for clinical use. In some instances production and initial purification of biologics, such as monoclonal antibodies for clinical trials is performed. All procedures conform to FDA specifications for biologic development and are in compliance with government regulations for human use products. The contractor also has the responsibility for development of master files and investigational new drug applications on biologics developed in BRMP, in other programs of NIH and in cooperation with extramural organizations supplying biologics for clinical evaluation.

Currently this contract provides for storage and distribution of approximately 100 different biologics in quantities ranging from two to 4,000vials for a given biologic. The contractor has produced a number of monoclonal antibodies in mouse ascites form, performed purification as well as general safety, pyrogenicity, endotoxin, mycoplasma, bacterial, viral and dosage testing on numerous monoclonal antibody preparations in preparation for clinical evaluation from within BRMP, other DCT programs, and from other divisions in NCI as well as extramural sources. The contract also has provided capability in the analysis and collection of information in preparation of master files and IND applications on cytokines and monoclonal antibodies for submission to FDA for clinical trial approval.

"This is the workhorse contract of our entire program," said Carl Pinsky, chief of the Biological Resources Branch in BRMP. There were no dissenting votes on the motion to approve the concept.

Shelf life evaluation of clinical drugs. Recompetition of a contract held by the Univ. of Georgia. Five years, estimated annual cost, $300,000.

To determine the suitability for use of drug products over extended periods of time, shelf life stability testing of the products is performed. FDA requires that all clinical drug products, including investigational drugs, undergo appropriate and extensive shelf life testing. As the sponsor of numerous investigational drugs, DCT needs the results of such shelf life tests conforming to FDA requirements to assure investigators of the continued suitability of the drugs undergoing evaluation.

Prior to 1982, DCT's contract manufacturers of clinical drugs attempted to perform shelf life testing on the various products. The results were mixed. To achieve a more thorough and complete shelf life evaluation of DCT's drugs, a separate resource contract to perform this function in accordance with the FDA guidelines was established. An RFP was issued and contract awarded to the Univ. of Georgia in 1982. All facilities and equipment, including four HPLCs, for use on this contract were provided at no cost to the government.

The contractor is currently conducting evaluations on over 110 separate lots of about 50 different chemical entities. The analytical methods used must be validated in a way acceptable to FDA. In accordance with FDA shelf life guidelines, samples of each lot are held at -10, 4, 25, and 50° C. Samples from each temperature are evaluated at the following time periods: 0, 3, 6, 9, 12, 18, 24, 36, 48 and 60 months. Cumulative reports are prepared at each time point on each lot and forwarded to DCT for review and filing with FDA in support of INDs. In addition, inspections of reserve samples that are retained on each lot are performed as required by FDA. Approximately 250 such inspections are performed each year. All of this information has proven to be extremely useful in identifying unstable drugs, documenting stable products, and determining the optimum storage condition for long term use.

Excellent data management is necessary to assure all testing is completed on schedule, and no samples are overlooked. Continuity of the ongoing shelf life tests is of high priority. In addition, it is expected that many new lots of drugs, including anti-AIDS drugs, will require shelf life testing by the contractor over the life of the contract.

There was little discussion and no opposition to the recompetition.

Procurement of fresh cells, monocytes, macrophages and T and B cell lines. Recompetition of a contract held by Bionetics Research Inc. Five years, estimated annual cost, $150,000.

The contractor has supplied to the investigators at the Laboratory of Tumor Cell Biology, large quantities of well characterized mycoplasma free tissue culture T and B cells, monocytes and myeloid cells, partially purified T cell growth factor (TCGF, IL-2), and radiolabeled nucleic acid and proteins for biochemical, biological and molecular growth studies.

These materials supply studies conducted by Robert Gallo's group.

The vote to approve was unanimous.

Phase 2 clinical trials of activated human leukocytes. Extension for an additional year of the studies, concept of which was approved by the board last February, for further studies of LAK cell/interleukin-2 therapy. The previously approved annual cost, for three years, was estimated at $3.6 million; the extension adds $900,000 to that amount.

The additional year was requested to provide appropriate phase in and followup in addition to the three years of accrual.

The proposal to study activated leukocytes, based on the results of Steven Rosenberg's trials in the Surgery Branch, was approvedin concept for three years of funding. When submitted, the plan was for three years of patient accrual, but no time was provided for phase in or phase out of the project. Due to the complexity associated with generating activated leukocytes, it was felt a two month phase in is appropriate. Because there is a high level of antitumor activity with this treatment, it was felt that a longer than usual phase out period is indicated to permit adequate followup of patients treated during the accrual period. That time should be 10 months. The time patients would be accrued to clinical protocols remains unchanged.

"I get more irascibile as the day goes on," board member Robert Goodman said. "Based on what we heard this morning (from Rosenberg, updating his results), that most of the responses are partial responses, and on the acute toxicity, this seems like a lot of money just for a pet of NIH."

"It's not a pet," Chabner bristled.

"We're looking closely at the results," Cancer Therapy Evaluation Program Director Robert Wittes said. "If it turns out that the renal results can't be duplicated soon, it's back to the drawing board."

"We won't spend $18 million without bringing it back to the board," Chabner said. "Twenty eight patients have been treated during the last two months. We'll know by July (if Rosenberg's results have been confirmed). You'll hear about it in October."

In answer to the question, what will be done if the results are negative, Wittes said, "We'll have to figure out why they are negative. If one accepts the Surgery Branch results on their face, and you can see the x-rays and cat scans, you have to consider why the other studies would be negative."

"You will have to develop a strategy for handling that, it's such a high visibility thing," Board member David Goldman said.

"In radiotherapy, everyone gets 35 percent results," Goodman said, still being irascible. Rosenberg's results overall have been about 35 percent, although almost 100 percent in treating kidney cancer. Goodman is a radiotherapist.

Despite Goodman's reservations, he did not oppose the motion to approve the concept, and it was approved unanimously.

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 Blair building room number shown, National Cancer Institute, NIH, Bethesda MD 20892. Proposals may be hand delivered to the Blair building, 8300 Colesville Rd., Silver Spring MD, but the U.S. Postal Service will not deliver there. RFP announcements from other agencies will include the complete mailing address at the end of each.

RFP NCI-CM-67876-16

Title: Computer based searches for chemical structures

Deadline: Approximately Aug. 15

This is a 100 percent small business set aside, the standard for which is annual gross revenue no more than $3.5 million.

The Div. of Cancer Treatment database includes chemical and biological information on approximately 400,000 compounds. There is a continuing need to perform high volume computerized full and substructure chemical searches of the database in support of various segments of the program: acquisition, compound screening and evaluation committees, National Drug Discovery Groups, and grantee requests.

The main responsibility of the contractor will be to support the needs of the Drug Synthesis & Chemistry Branch for high volume substructure, full structure and data item searches. The contractor shall analyze each request, develop appropriate search strategy, making full use of the system's capabilities, phrase the search question, interactively process the query, check output via graphic terminal for accuracy, completeness, and relevancy, and generate the output report. The contractor will also generate systematic nomenclature on selected compounds.

The principal investigator should be trained in organic chemistry at the master's level, should have additional training in chemical documentation and retrieval, and should have at least four to five years experience in chemical information retrieval and substructure searching. There should be an additional chemist at the master's level, with chemical nomenclature knowledge and experience, available to the project for four to eight hours a week.

The contractor will perform the tasks on site, at the Developmental Therapeutics Program offices in Bethesda, as requested. The government will provide appropriate space and equipment for performance.

The contract period will be five years, beginning approximately June 15, 1987. One cost reimbursement contract is expected to be awarded. This is a recompetition of a contract currently held by Maxima Corp. of Bethesda.

Contract Specialist: Patricia Shifflett
RCB Blair Bldg Rm 216
301-427-8737

NCI CONTRACT AWARDS

Title: Biomedical computing--design and implementation (for Radiation Epidemiology Branch)
Contractor: Information Management Services Inc., $1,231,465.

Title: St. George cancer screening and clinical research project
Contractor: Univ. of Utah, $700,000.

Title: Tracing individuals for environmental epidemiologic studies of cancer using vital statistics records
Contractor: Westat Inc., $116,549

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

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