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HAMMER SAYS PRESIDENT'S SCIENCE ADVISORY TO ASK FOR FY 1985 SUPPLEMENTAL APPROPRIATIONS FOR NCI

President's Cancer Panel Chairman Armand Hammer said Monday that George Keyworth, director of the White House Office of Science & Technology Policy, had agreed to ask President Reagan to consider seeking a 1985 supplemental appropriations for NCI. Hammer said Keyworth told him of that intention during a meeting last week in which Hammer expressed concern over the loss of 150 NCI grants and

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In Brief

LAIRD MYERS HEADS AACE, GEORGE HILL PRESIDENT ELECT; CAL TECH'S HOOD RECEIVES BERTNER AWARD

W.P. LAIRD MYERS, Eugene Kettering Professor at Memorial Sloan-Kettering Cancer Center and associate dean for education at Cornell Univ. Medical School, is the new president of the American Assn. for Cancer Education. George Hill, director of surgical oncology at UMDNJ-New Jersey Medical School, is president elect. Stephen Stowe, director of radiation oncology at New Jersey Medical School, has been reelected secretary of the association. Beverly Raney, Childrens Hospital of Philadelphia and Univ. of Pennsylvania Medical School, was reelected treasurer.... **CONGRESSMAN DON PEASE** (D.-Ohio) has introduced a bill to ban the import of benzidine, its salts and benzidine containing products. The bill supports a world wide ban of the chemical, recognized for many years as a potent carcinogen.... **LEROY HOOD,** director of the California Institute of Technology Cancer Center, received the 35th annual Ernst W. Bertner Memorial Award this week for his research on the genetic aspects of immunologic recognition. The award was presented at the annual Symposium on Fundamental Cancer Research at M.D. Anderson Hospital. Jeffrey Drebin, Harvard Medical School, received the annual Wilson S. Stone Memorial Award for outstanding achievement in the biomedical sciences accomplished by a student in the U.S..... **CHARLES LEMAISTRE,** president of the Univ. of Texas System Cancer Center, has been made an honorary member of the American Pharmaceutical Assn..... **ROBERT HUBEN** has been appointed chief of the Urologic Oncology Dept. at Roswell Park Memorial Institute. He has been serving as acting chief since last year.... **DIETARY VITAMIN** D and calcium intake appear to be related to a reduced risk of colorectal cancer, Univ. of California (San Diego) investigators reported in a recent issue (Feb. 9) of "Lancet." Cedrick Garland, assistant professor of community and family medicine, and his colleagues found in a study of 1,954 men that those who frequently consumed foods rich in vitamin D and calcium had a rate of colorectal cancer almost one third that of those who rarely consumed such foods.

CENTER DIRECTORS, OTHERS TELL PANEL ABOUT THREAT POSED BY SPENDING CUTS

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$40 million through the order by the Office of Management & Budget to forward fund enough grants with 1985 money to slash the total of new and competing NIH grants from 6,500 to 5,000.

"We found him sympathetic to our concerns," Hammer said Monday during the Panel's meeting at Wistar Institute in Philadelphia.

"I don't need to emphasize to this group the seriousness of those reductions," Hammer said. Other problems which are having a negative effect on the Cancer Program, Hammer said, include reductions in the number of positions allocated to NCI and the issue of reauthorization of the National Cancer Act.

Both Hammer and Panel member William Longmire are constituents of Congressman Henry Waxman, chairman of the House Health Subcommittee which is responsible for writing health legislation. It was Waxman's version of the vetoed biomedical research authorization bill last year which stripped some of the NCI director's authority from the National Cancer Act. Hammer said he and Longmire planned to meet with Waxman to urge quick approval of a new reauthorization bill which would leave NCI's authority intact.

Hammer said he could not resist passing on to Keyworth information he had learned about the very early results of a study being conducted by Stephen Rosenberg, chief of the Surgery Branch in the Div. of Cancer Treatment's Clinical Oncology Program. This study involves the use of T-cell growth factor in cancer treatment, an idea growing out of Robert Gallo's laboratory. Hammer said Rosenberg had obtained "complete disappearance" of cancer in a patient with advanced carcinoma of the colon, including lung metastases. Another patient, with melanoma, was treated with the same process, with complete remission of the primary tumor and apparent clearing of lung metastases.

"I asked Dr. Rosenberg what he needed," Hammer said. That's a question that has ended up costing Hammer money when he's asked it in the past, and this was no exception. "He said he needed money, and another technician. He said that with another $100,000, he could put four more patients into the study. Dr. (Vincent) DeVita (NCI director), said that the Institute could accept gifts, so I decided to make another $100,000 award." Earlier this month, Hammer presented $100,000 to Gallo and three Japanese scientists as the annual Armand Hammer Award for Outstanding Research in Cancer.

Hammer indicated he did not intend to let the federal government off the hook with that extra award. "Here we are, battling for extra money, when the Defense Dept. has no problem getting billions for dreadnaughts." He said he proposed to Keyworth that the government do for cancer "the same thing we did with NASA. Let's make billions of dollars available, and bring the best scientists together, rather than struggle along, battling for a few dollars. I believe that with the coordinated support of the President, we can lick this dread disease."

That message was greeted enthusiastically by the cancer center directors and other scientists at the Philadelphia meeting.

Hilary Koprowski, director of Wistar Institute, said "the fate of Wistar's basic cancer research program is strongly dependent on the funds made available to NCI and the research priorities established by NCI... We cannot afford to suddenly dismantle major aspects of a research institution in which there has been a long term investment in resources, primarily human resources. That appears to me to be the greatest danger inherent in decreased funding of NCI--the inevitable dispersal of human resources assembled at the cancer centers which would result from decreased funding from NCI."

The forward funding of grants and subsequent reduction jeopardizes from five to 10 of the approximate 30 Wistar NCI grants being competed this year, Koprowski said. "How can a viable productive research program be planned and managed when federal government priorities change with such suddenness? The message must be delivered to the Administration and Congress that OMB's action on the NIH budget will have a disastrous effect on the NIH extramural research program."

Koprowski described Wistar's development of monoclonal antibodies reacting with cancer of the stomach, pancreas and colorectum. More than 120 patients at collaborating American Oncologic Hospital in Philadelphia and the Cancer Institute in Nantes have been treated with those monoclonal antibodies. So far, three patients with colorectal cancer and one with pancreatic cancer have had complete disappearance of tumor, 50 per cent had transient responses and 20 per cent with more permanent responses. Those were from single injections of a single monoclonal antibody, and there were no adverse effects, Koprowski said.

Koprowski said the time has arrived for studies using several monoclonal antibodies at once, with multiple injections. "There are monoclonal antibodies available in different laboratories which are sufficiently studied to be used now in humans afflicted with 10-15 different cancers. Several reasons contributed to the nonavailability of these for immediate clinical applications:

"1. Timidity or fear of responsibility on the part of the inventor.

"2. Intrinsic management inertia generated by a novel approach to treatment of cancer patients; i.e., human experimental ethics, IRB and other committees in hospitals.

"3. Lack of funds to produce sufficient amounts of potent, endotoxin free, purified sterile monoclonal antibodies to be applied clinically in immunotherapy trials.

"4. Lack of coordination of information concerning characteristics of the available monoclonal antobidies.

"A trial with a number of patients which would supply statistically meaningful results will cost approximately $2 million. If we organize 10 such trials, a sum of $20 million is necessary to push the project of monoclonal antibodies in cancer therapy to a stage where cancer cures by immunotherapy will become convincing. We need to scale up our efforts now instead of scaling down the wonderful opportunities provided by basic science to put the final nail in the cancer coffin."

Peter Magee, director of Fels Research Institute, noted that 81.3 per cent of Fels' budget was in the form of competitively awarded grants, most of them from NCI. If NCI's budget remains static or decreases, within three years that percentage would shrink to 51.3, Magee said. That would leave as "unknown" the source of 30 per cent of the Institute's budget, which would be "disastrous."

Magee said Fels is precluded from undertaking private fund raising efforts because of its relationship with Temple Univ. The most likely solution to a major funding shortfall would be that Temple would establish a new department and place senior Fels faculty on the Temple faculty.

DeVita commented that the multiyear funding of FY 1985 grants with 1985 money did not affect those being competed in the first cycle of the year, when grants were funded to a priority score of 170. In the second cycle, grants for Philadelphia institutions—Fels, Wistar, Fox Chase, Temple, Univ. of Pennsylvania—would be affected by multiyear funding in the amount of $1 million, DeVita said. Another $1 million probably would be lost in the third cycle.

"That's depressing news," Longmire said. Hammer suggested that the Philadelphians contact members of the Pennsylvania congressional delegation, particularly Sen. Arlen Specter, who he said has expressed interest in the cutbacks.

Dani Bolognesi, Duke Univ. Comprehensive Cancer Center, addressed the Panel on progress in AIDS research, which has been spearheaded by NCI. Bolognesi noted that NCI has been required to spend more than $50 million on AIDS since 1983 but has received only $5 million in supplemental funds for that purpose. NCI has had to reprogram money from other areas to meet the AIDS mandate. "We're consuming our own resources," Bolognesi said. "Now, with the new directive (multiyear, or forward, funding) we will have to subtract another $40-50 million. With Vince DeVita's very able leadership, keeping the pressure on the pumps, the water is starting to reach the fire. Now is not the time to reduce the pressure."

"There is a myth afoot that needs to be stamped out," DeVita said. "That is, that because we are so big, NCI can absorb anything... We were expected to reprogram $15 million this year (for AIDS). We don't have enough bad programs to do that anymore."

Allan Goldstein, chairman of the Dept. of Biochemistry at George Washington Univ. School of Medicine, presented the Panel with a resolution passed by the Assn. of Medical School Depts. of Biochemistry. The resolution said the OMB ordered cutback would "thwart the peer review system... diminish productivity and markedly affect the morale of the scientific community... (and) freeze out highly talented young investigators, essential to our ability to exploit recent dramatic developments in the biomedical sciences."

Goldstein added, "Lack of adequate funding will delay the full application of some of the most important biomedical research developments in cancer and in other areas and will seriously restrict our ability to train the next generation of scientists necessary for the discovery of new knowledge."

Goldstein urged that to overcome long term problems resulting from "a tragic decline in federal support," these steps be taken:

1. Establish a significant number of new PhD graduate training programs in each of the biomedical disciplines to encourage graduate students to enter science as a career.

2. Restore the funding for the 1,500 grants that will be lost in 1985.

3. Encourage the President to develop new legislation to mandate the percentage of scientifically approved investigator initiated research grants be restored to the funding level it was in the mid 1960s. "This would require a doubling of the current funding for extramural biomedical research, i.e. from about $2 billion to $4 billion. While this is a formidable increase, it is small compared with our annual health care bill of more than $300 billion which is increasing by $20-30 billion a year as our population ages."

Richard Cooper, director of the Univ. of Pennsylvania Cancer Center, noted that "the costs of conducting modern cancer research have far outdistanced inflation. But the payoff has been incredible... Things are not simple. Progress is not easy. Interdependencies are not recognized, nor

are collaborations established overnight. What we now have is a highly integrated, highly energetic national effort in cancer research that is bearing fruit at an astonishing pace. This complex superstructure, while unprecedented in the history of the world, is extraordinarily fragile. It is nothing more than people... You have asked whether we could withstand a flat NCI budget for two or three years. I think it is clear... that we simply could not. Not without disrupting research momentum, dismantling networks that took years to establish, not without seeing young people further discouraged from continuing their careers in research...Ours is still a frontier nation, and the frontier is scientific discovery and the eradication of diseases which afflict members of our society. Only the federal government can provide the necessary fuel to sustain this research momentum."

John Durant, President of Fox Chase Cancer Center, said the National Cancer Program "is clearly a federal responsibility. Any notion that other entities will come in with significant amounts of money is fragile."

Durant referred to what he said were cutbacks in NIH funds in the 1960s through rescisions, and in the 1970s through impoundment. "Now in the 1980s we have forward funding. We've lived through these problems before, when logic has prevailed (and the funds restored, through legal or other action). Cutbacks in biomedical research funding discourage young people from entering the field, Durant said. "It is usually the smartest people who are the quickest to get the message, and they take their smarts elsewhere." The budget cut "is cutting off our noses to spite our faces, and we are likely to wound ourselves much more severely than in the feet."

John Ultmann, director of the Univ. of Chicago Cancer Center and president of the Assn. of American Cancer Institutes, said the cutbacks come "at a time in history when science is poised to answer some of the most fundamental questions in biology and to make some of the most far reaching discoveries to solve problems bearing on disease and its prevention and cure... (The cuts) will have an immediate crippling effect on current research and a long term, detrimental effect on recruitment of the next generation of scientists, on the quality of plants in which research is done, and on the tools with which discoveries are made."

Ultmann reviewed major areas of progress made in cancer research since the National Cancer Act of 1971 increased amount of federal support. He noted that an increasing preoccupation with defense and deficits has reduced federal support for cancer research despite the cost of the disease to the economy of $11 billion a year in medical expenditures and $13 billion in lost wages. He referred to the threat to the goal of reducing cancer mortality 50 per cent by the Year 2000 posed by the budget cuts and ignoring of the FY1986 bypass budget.

Ultmann offered as recommendations of AACI, the American Society of Clinical Oncology and other organizations:

1. The highest priority is to accomplish reauthorization of the National Cancer Act.

2. Line item authorizations for cancer programs in appropriations bills.

3. Reversal of the forward funding directive.

4. Repair of the biomedical research infrastructure, facilities and instrumentation.

Displaying on a slide a cracked, egg shaped drawing showing the interrelationship of basic and clinical research, Ultmann said, "This is the egg laid by the golden goose. It's fractured, and there ain't going to be no chicken out of this egg."

He could have added, as long as he was mixing up his species of poultry, that the egg was cracked by the turkeys at OMB.

Jonathan Rhoads, professor of surgery at the Univ. of Pennsylvania and the first chairman of the National Cancer Advisory Board, said that deferring expenditures in cancer research now "is not likely to save money in the long run but, on the contrary, is likely to lead to more rapid expenditures later ... What has been achieved is a rich reward for that which has been spent and there are many reasons for believing that the remarkable growth in basic knowledge, if cultivated and fostered, will yield even greater rewards to the American people in the years to come."

DCT BOARD APPROVES NEW SCREENING PROGRAM, NATURAL PRODUCT CONCEPTS

The Board of Scientific Counselors of NCI's Div. of Cancer Treatment has approved the plan to phase in use of human tumor cell lines in DCT's drug screening program. The plan, initiated by DCT staff, grew out of recommendations of an international workshop at NCI in January and followup discussions among staff and a BSC committee chaired by Mortimer Elkind.

The Board also went along with the theme developed by DCT and its advisors that, rather than trying to get any definite number of new compounds into clinical testing every year, the Drug Development Program should emphasize quality. "We would like to seek a focus more on the qualify of compounds," Michael Boyd, director of the Developmentla Therapeutics Program, said. "We should be very critical of compounds before we take them to the clinic. A compound ties up a lot of money once it gets to clinical trials."

Approval of the new screening system is contin-

gent on demonstration of its feasibility over a two year period. Assuming the new system is feasible, increased sensitivity it is expected to provide opens the way for resuming screening of natural compounds, dropped from the program about three years ago because the existing screens were unable to find much activity in them. The Board gave concept approval to a package of contract supported natural product projects totaling an estimated $2.5 million a year; the contracts will be awarded only if the new system is implemented.

The new system will be a disease oriented screening approach as has been established with the Lung Cancer Drug Discovery Project initiated last year. It will use an in vitro cell line prescreen, with active compounds going on to in vivo tests with murine and human tumor models. The NCI Decision Network Committee will determine from those tests which compounds will go into clinical trials.

The new system will be established in parallel with the existing in vivo P388 prescreen, the latter screening 10,000 compounds a year and the in vitro system 2,000. In 1985-86, the in vitro system will utilize 20-30 human lung cancer cell lines. In 1986-87, that will be expanded to include five to eight lines each of human colon, breast and prostate cancer cell lines. If the system is taken to full implementation in 1987-88, the panel will be expanded to include one to two lines each of ovarian, melanoma, leukemia/lymphoma, brain, sarcoma, renal, gastric and hepatoma tumors.

In 1986-87, according to the phase in plan, the emphasis will shift from the P388 to the in vitro prescreen, each handling about 6,000 compounds.

Compounds proposed to be screened during initial development and implementation of the in vitro/in vivo screening project from 1985-87 include:

1. Compounds active in current screens but tested and found inactive in the clinic—i.e., will the new screen better predict true (clinical) negatives?

2. Compounds active in the current screen and tested and found to be active in the clinic—i.e., is the new screen at least as good as the current screen in detecting true (clinical) actives of this type?

3. Compounds found negative in P388—i.e., can the new screen detect new kinds of potential anticancer agents that would have been missed by the P388? To facilitate a timely comparison of the screens, during 1985-87 a total of 8,000 new agents will be screened in parallel using both the P388 and the cell line prescreens. As an alternative, or in addition, a group of available compounds can be selected from NCI's existing repository and evaluated in the new screen. In effect, they are "new compounds" to the new screen.

Boyd said the in vitro work would be done by DCT at the Frederick Cancer Research Facility, with its "critical amount of expertise" available there. The in vivo work will be done as it has in the past, through contracts.

"If it should be the case in any particular year that no compound goes to the clinic, there should not be a feeling of failure," Board member Alan Rosenthal said. "It is more likely in that event that you are doing your job."

Enrico Mihich, member of the National Cancer Advisory Board who participated in the discussion, commented that the system may turn up active drugs without information on its specific mechanism of action. He also suggested that an effort should be made to develop models for testing drugs active against metastatic tumors.

Boyd noted that the new national Drug Discovery Groups are addressing those problems. "Metastatic models are very important, and we are taking a poke at it in a limited way with the Lung Cancer Drug Discovery Project," he said.

Boyd said concept approval for the new natural product contracts was needed now, "to get the wheels rolling" in anticipation of full implementation of the new system. Board member Efraim Racker objected, calling it "a fishing expedition" which should await demonstration of the new system's efficacy.

"If you want to call it a fishing expedition, that's all right with me," Boyd said. "That's the definition of screening."

"I've done many fishing expeditions myself," Racker said. "The question here is, will we get a return on this? I'd like to see something more rational." DCT Director Bruce Chabner responded, "We are putting a lot of money into the rational synthesis of compounds. The Drug Discovery Groups are doing that, and we are supporting them with $2.5 million a year. Plus about 40 per cent of our grants are doing that. But the most effective drugs that reach the clinic are natural products." Boyd added that $20 million of the DTP budget goes into the rational design of drugs.

Racker was not convinced and cast the only vote against approving the concept for the natural product contracts.

The natural product concepts as proposed by DCT follow:

Algal fermentations. Estimated annual cost, $250,000, three years. Staff description:

The algae are a diverse group of simple photosynthesizing plants which have only been sparsely investigated from a chemical viewpoint. The blue-green algae are of particular interest because of three very recent observations which relate to cytotoxicity and/or antitumor activity. First, Moore's group at the Univ. of Hawaii has isolated active agents of novel structure types from at least

three blue-greens in the past two years. The quantities have been very limited, however. A second observation made by several marine chemists is that antitumor or cytotoxic activities of certain sponges seem to correlate more with the microflora found inside the sponges than with any other factor and the most active microflora seem to be blue-green algae or related organisms. The third intriguing observation is that significant in vivo antitumor activities were seen in various mosses but the activity of recollections for fractionation studies has been quite erratic. Recent microscopic examination of these samples has shown a good correlation between the abundance of blue-green algae and antitumor activity.

The indications are that blue-green algae may be an exciting source of antitumor agents and a project is needed to investigate this. Because these are microscopic or barely macroscopic organisms, the science requires development of fermentation technology to produce the quantities needed for serious drug development as well as considerable expertise in algal culture, a small highly specialized field.

The project will have two main objectives: the isolation, culturing and scale up of algae from active leads already in hand which are suspected to be algally related and, secondly, the isolation and small scale culturing of algae from a variety of marine and terrestrial sources and the preparation of extracts for screening by NCI. The project will generally exclude or deemphasize the massive brown and red algae which have already been studied chemically.

It is currently estimated that there are 10-20 plant and marine leads with antitumor or cytotoxic activities that have a good probability of being due to algae and there is a wide literature about the co-occurrence of algae with higher organisms which would serve as a basis for collection of materials from which to isolate algae. We would expect to isolate and ferment 200 algae per year on a small scale sufficient to obtain enough material for screening and another 10-15 on a larger scale suitable for chemical isolation.

Fermentations of marine organisms. Estimated cost, $250,000 per year, three years.

Micro-organisms, especially actinomycetes, are the most prolific source of new antitumor agents and antibiotic substances discovered thus far. Other types of micro-organisms have been much less studied and the overwhelming majority of all micro-organisms isolated have been from soil samples. Until fairly recently little attention has been paid to the marine environment as a source of drugs, and marine micro-organisms have just been taken under serious study in a few laboratories. The techniques of growing marine micro-organisms are rather specialized and generally require relatively low temperatures, high salt concentrations and supplements of materials of marine origin such as fish meal or chitin to provide trace nutrients. While some work has been done with marine muds, this has been scanty and micro-organisms from other areas of the marine environment such as those found in association with marine plants and animals have not been touched. Other habitats of interest would include mangrove flats, estuaries, bays and tidepools where the varying concentrations of nutrients and differences in salinity provide substantial habitat differences which are exploited by those organisms best adapted to the situation.

The purpose of this project is to isolate, ferment and prepare extracts of 500 marine micro-organisms per year for deposition in the repository and subsequent screening by NCI, and to scale up five to 10 of these fermentations per year to a level adequate for chemical isolation work.

Collection and toxonomy of marine organisms. Estimated cost, $700,000 per year, five years.

The marine environment is a tremendously varied and rich habitat which has been little explored as a source of drugs. Over half of the Phyla of the animal kingdom are recognized as being exclusively marine, and it is readily apparent from the limited literature in the marine natural products field that the chemical types of the secondary metabolites produced are quite different from those of the terrestrial plants, animals and microbes. Because 98 per cent of the ocean is a nutrient poor desert, marine life congregates in the nutrient rich areas near land, and there is an intense competition for food and living space which is a kind of chemical warfare among species, involving the production of a wide variety of offensive and defensive toxins, repellants, attractants, and camouflages. The production of so many biologically active compounds, many designed to kill or incapacitate other species, speaks well for the likelihood of discovering compounds with the ability to selectively affect the growth of some types of tumor cells.

NCI has previously screened about 15,000 extracts of marine organisms, mainly using the P388 leukemia as the primary screen, and has found several interesting leads, one of which, didemnin B, has recently entered clinical trial. The greatly increased sensitivity of the human tumor cell lines compared to in vivo testing should lead to a substantially increased rate of discovery of new agents. This is not an easy project because of the difficulties of logistics of collection, the relatively high expense of boat time and shipping and the scarcity of good marine taxonomists. To date there have been no industrial drug discovery projects in the marine area in the U.S., and the marine environment, despite its high potential for discovery of interesting compounds, remains an orphan area of drug research.

The objectives of this project are to collect sufficient quantities of about 2,000 marine organisms to supply 10 gram samples of extract after processing by a separate extraction facility. In addition to the above general samples for screening, the contractor will be required to make 40-50 large collections of 200 kg each of active organisms for fractionation, isolation and characterizations of the active components. All materials submitted will be taxonomically identified to the extent

possible.

The collections will mainly be concentrated in the prolific tropical and semitropical waters of the Western Pacific Ocean (Australia, New Guinea, Phillipines, China) with secondary locations in the Indian Ocean (East African Coast, India, various island groups).

Plant collection and taxonomy. Estimated cost, $700,000 per year, five years.

Plants have been a major source of new drugs for thousands of years and have yielded a number of clinically active antitumor agents including the vinca alkaloids, indicine N-oxide and homoharringtonine as well as the basic structural leads for the epipodophyllin glycosides VP-16 and VM-26. A wealth of other active, novel structure types have been discovered which are undergoing modification in laboratories around the world and which have good potential for eventual production of clinically useful analogs. These include ellipticine, camptothecin and maytansine.

The large number of plants screened to date for anticancer activity represents only 10-20 per cent of those available and there are large areas of the world with unique flora that have never been examined, including particularly China, Southeast Asia and rain forest areas in Africa and South America. The availability of these resources is rapidly declining as civilization continues to encroach on virgin areas so the time of this project is very important.

CONCEPT REVIEW FIGURES ARE ESTIMATES ONLY: RFPs, RFAs NOT YET AVAILABLE

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 based 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.

The use of human cell lines in an in vitro screening battery will increase the sensitivity of detection of activity at least 100 fold over in vivo screening and will permit detection of many active compounds which were previously missed as well as compounds having high specificity for particular human tumor types. Further, the screening of crude extracts results in a wide variety of compounds being tested simultaneously which will give rapid feedback on the capabilities and selectivity of the screening models.

The project will acquire approximately 2,000 plant samples per year in quantities sufficient to yield 10 grams of extract per sample for immediate screening use and for deposition in a repository for use in future new screens.

All of the samples will be definitely identified by qualified taxonomists and the contractor will input identifying data to NCI. The contractor will also make re-collections of 60-80 active plants per year in quantities of 100 kg each for chemical isolation of the active components.

The screening data generated from this project will be analyzed by NCI staff and will be used to guide future accessions of plant materials for the screens. Because the screening systems to be used are a novel approach, it has been decided not to bias the results by ab initio selection of plants to be screened or not screened. The selection of floristic areas which have not been screened previously enables the collection of a large amount of totally new plant material as well as a sufficient number of previously screened plants to permit analysis of the efficacy of the new screening systems relative to the P388 leukemia in vivo. A variety of sources will be used by the contractor to search out plants with reported folklore activity and to be sure that such plants are included in the collections.

Natural products extraction laboratory and sample repository. Estimated cost, $300,000 per year, five years.

Other proposed new projects will collect about 7,000 new samples of plants, microbial extracts and marine organisms per year. Ongoing projects for evaluation of fungi and collaborations with various groups in universities, research institutes and industry will acquire another 2,000-3,000 samples per year. This contract is proposed to receive the materials shipped from around the world, to prepare extracts in a suitable form for screening, to store these extracts under optimal conditions and to ship them to the screening laboratory on request from NCI staff. The contractor will also be responsible for organization of the samples for easy access and keeping a computerized inventory of all samples on hand.

A good repository of natural product extracts for present and future screening is a key component of a long term drug discovery effort. Past projects in natural products were focused only on collection and extraction of sufficient quantities of material to conduct initial screening in the P388 leukemia system, and not on future needs or the possibility of new screens and the consequent desire to rescreen negative samples in other systems. The proposed effort in collection will enable enough samples to be prepared in adequate quantities so that future collection efforts can be scaled down and sample quantities for most future needs can be met from the repository.

Because the laboratory for screening the samples in the human tumor cell lines will be located at the Frederick Cancer Research Facility and frequent shipments to the screening lab will be required, it is desirable to locate this project at FCRF if space is available, or otherwise at another location in the Washington D.C. area.

Extraction protocols will be provided by NCI staff and all extracts will be stored as multiple

aliquots under frozen conditions to provide for easy use. Extracts will be coded such that their origins will be accessible which will enable selective testing to be carried out to follow up leads. Thus, if a particular extract showed interesting activity, it would be possible to locate extracts of other species from the same genus or family to screen for better producers of the activity of interest or producers of related activities.

Isolation of novel antitumor agents. Estimated cost, $300,000 per year, three years.

The proposed plant and marine collection projects, together with the various new and existing fermentation projects will generate approximately 5,000 crude extracts annually which will be screened against the human tumor cell line panels at FCRF. It is anticipated that active extracts will fall into two categories, namely those exhibiting broad cytotoxicity against most or all of the cell lines used, and a limited number which will show some form of selected activity. The latter category might include extracts possessing activity against a single subtype of a particular tumor, those showing selectivity between different organ tumor lines (e.g. lung vs. breast, colon, etc.) or those with activity against a particular tumor class (e.g. adenocarcinomas).

The extracts in the first category (generally cytotoxic) while being considered of lower priority, would lead to the isolation of compounds having unusual biochemical pathways and cellular processes. The fractionation of such extracts could be guided by any of a variety of assays using readily available tumor cell lines and could be given to suitable external research groups for the isolation of the active compounds on a research grant or cooperative agreement basis. Extracts exhibiting selective action would be considered of the highest priority and would require rapid fractionation using the relevant cell line only available at FCRF. In order to achieve this objective, the establishment of an in house isolation group based either at Bldg 37 or FCRF is proposed. Such a group would comprise four to six experienced natural product chemists led by an expert in the field, and would concentrate solely on the isolation of the particular compound or compounds responsible for the selective activity observed. The absolute necessity for the establishment of such a group is dictated by a number of important factors. Because of the highly selective activity, only that cell line in which such activity was initially observed would be suitable for the subsequent bioassay guided fractionation. Such a process, involving assays performed at FCRF for a distant group, would involve long turnaround times due to mail delays. The alternative procedure of distribution of relevant cell lines to distant groups would be impractical and wasteful due to long delays in the startup of the line, and the probability that the particular line would only be needed for one particular isolation project.

RFPs AVAILABLE

Requests for proposal 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. 20205. 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-CP-EB-51029-13

Title: Support services for biochemical epidemiology

Deadline: Approximately May 5

The Environmental Epidemiology Branch and the Laboratory of Human Carcinogenesis of NCI's Div. of Cancer Etiology is soliciting proposals from qualified organizations for support services for biochemical epidemiology projects. The contractor shall provide the following services:

1. Assist in the identification and selection of high quality laboratories capable of performing laboratory assays.

2. The collection, shipment, processing, distribution, and short term storage of a wide variety of biological specimens, including whole blood serum, plasma, red and white blood cells, urine, feces, saliva, and tumor tissues.

3. The performance of at least some of the assays required under this project.

The contractor shall also be responsible for the negotiation, award, and monitoring of subcontracts, on a large scale, for the purchase of a broad range of serologic, hematologic, bacteriologic, virologic, molecular, enzymatic, micronutrient, and exposure related assays. Additionally, the contractor shall be responsible for recording the data provided by the subcontractors in a systematic fashion to permit NCI to computerize the results.

This contract will be a 100 per cent small business set aside, the size standard for which is 500 employees.

The concept from which this RFP was derived was approved by the DCE Board of Scientific Counselors last fall and was reported in the Nov. 9 issue of The Cancer Letter, page 4.

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