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WEICKER NEGOTIATING FOR 6,000 NIH GRANTS IN BOTH 1985, 1986; SOCIETIES APPEAL FOR ADEQUATE FUNDING

Sen. Lowell Weicker (R.-Conn.) revealed at a hearing of public witnesses before the Labor-HHS Appropriations Subcommittee which he chairs that he is close to an agreement with the Senate

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In Brief

HENNEY TO LEAVE NCI FOR KANSAS; DAN LONGO HEADS BRMP; DEVITA TO RECEIVE NERVI AWARD

JANE HENNEY, NCI deputy director, will leave that position July 1 to join the faculty and medical staff of the Univ. of Kansas Medical Center in Kansas City. Henney's departure was occasioned by the fact that her husband, Robert Graham, will leave his position as head of the Health Research & Services Administration to become executive vice president of the American Assn. for Family Practice which is headquartered in Kansas City, Mo., his home town. Both will start their new jobs Sept. 1 after a two month vacation. Henney has been NCI deputy director since Vincent DeVita became director in 1980, first in an unofficial capacity and then, in 1982, with the official appointment. Graham, before becoming HRSA administrator, served two years as staff director for the Senate Health Subcommittee when it was chaired by Edward Kennedy.... **DAN LONGO,** who has been chief of the Experimental Immunology Section of the Div. of Cancer Treatment Medical Branch, has been named associate director and head of the Biological Response Modifiers Program by DCT Director Bruce Chabner.... **MARVIN RICH,** director of AMC Cancer Research Center in Lakewood, Colo., for the past four years, has been named to the additional position of president of AMC. As chief executive officer and director, Rich will oversee the administrative as well as scientific programs of AMC. He succeeds Manfred Minzer, who has retired as president.... **CORRECTION:** The Northern California Cancer Program was incorrectly identified in **The Cancer Letter** April 19 as "Northern California Oncology Program." That was an inappropriate amalgamation of names of the consortium cancer center (NCCP) with the regional cooperative group, the Northern California Oncology Group, which operates as a clinical research activity of the center.... **VINCENT DEVITA** is in Rome where he will receive the second annual Pier Luigi Nervi Award for outstanding contributions to cancer treatment. The award will be presented at Vatican City May 15, possibly by Pope John Paul II. DeVita will give the keynote address May 17 at the Rome International Symposium on the Challenge of Local Tumor Control and its Impact on Survival. The Nervi Award was established by radiotherapist Carlos Nervi in memory of his father, the late, internationally renowned architect.

WEICKER OKAYS 6,000 GRANTS FOR 1986 IF HE CAN GET THE SAME FOR THIS YEAR

(Continued from page 1)
leadership on a proposal to fund 6,000 new and competing renewal NIH grants in both the current and 1986 fiscal years. Key figure in the negotiations is New Mexico Sen. Pete Domenici, chairman of the Budget Committee. The Budget Resolution, which sets spending limits for FY 1986, was being debated this week in the Senate, with a tentative schedule for a final vote on May 9.

Weicker and Sen. Daniel Inouye (D.-Hawaii) had ready an amendment to the resolution that would have provided for funding 6,500 grants in FY 1986 as well as maintaining NIH funding in general at 1985 levels, plus inflation. Implicit in the amendment would be a rollback of the White House plans to chop the 1985 budget through multiple year funding of a substantial number of competing grants. That would reduce the number of competing grants funded in 1985 from the 6,500 approved by Congress to 5,000.

In his negotiations with Domenici, Weicker agreed to hold the number of grants in 1986 to 6,000, provided the same number is funded for 1985. That would not completely overcome the effects of the OMB strategy but would double the additional 500 the Administration had said it would accept.

Negotiations were still going on at **The Cancer Letter** press time.

Representatives of three major cancer organizations appealed to Weicker's subcommittee for a substantial increase in NCI's budget.

Timothy Talbot, former president and chairman of the board of the Assn. of American Cancer Institutes, and Albert Owens, speaking for the American Society of Clinical Oncology, both asked for $1.46 billion, the amount requested in NCI's 1986 bypass budget.

Gerald Murphy, immediate past president of the American Cancer Society and present chairman of its Public Issues Committee, noted that ACS previously had recommended $1.5 billion for NCI. Murphy suggested that, in view of the national deficit problem, that amount could be scaled down to $1.3 billion provided "everyone involved . . . find prudent ways of spending a little less."

Talbot, who is president emeritus of Fox Chase Cancer Center, said that "stable support of research endeavors and education are not some abstract game for a few people to play, but are the foundation and source of the nation's strength . . . There are several important facts that need to be made visible:

*"Recent actions of OMB have already led to what is called a mixed bag. Four centers, whose renewals were awarded in the first cycle of 1985 received 95 per cent of the peer review recommended funding levels. The seven centers who were in the second cycle have been told that for now they should count only on receiving a five per cent increase over their current levels. This resulted in part from NCI being forced to forward fund one center for three years. If this process continues there will obviously be even greater injustices in the future, as well as considerable harm.

*"Since 1976, there has been no growth in constant dollars for NCI. Since 1980, the level of support has been seriously reduced. In 1983 it was below the 1974 level. This is a serious threat to our research endeavors.

*"Cancer research has been cost effective. The saving of useful productive lives has saved more money and also produced much more money than has been spent, as documented by Dr. Emil Frei and others. The ratio of savings to expenditure may be as high as 15 to 1 or more.

*"There are other economic justifications for the support of research, as exemplified by the billions of dollars of revenues from applied technology resulting from biomedical research.

*"Significant progress has been made and will continue to increase. We support the position of Dr. Vincent DeVita which states the goal of reducing cancer mortality 50 per cent by the Year 2000. There is reason to believe that this can be done, but not without stable support."

Talbot emphasized three AACI requests:

*Cancer center support grants should be fully funded, as demanded by Congress in the report accompanying the 1985 appropriations bill.

*The NCI bypass budget of $1.46 billion "should be the minimum amount appropriated."

*"The sciences are all greatly interdependent; therefore, we also strongly endorse the recommendation of the ad hoc Committee for Biomedical Research that $5.6 billion should be made available to NIH."

Owens, director of the Johns Hopkins Oncology Center and speaking for ASCO, said the society stands with "the newly established National Coalition for Cancer Research in support not only of the continuation of the National Cancer Act, but.. for full funding of the bypass budget for NCI of $1.46 billion. Your committee and the entire Congress has strongly supported the National Cancer Institute's programs in the past, and you and your colleagues should be credited with some of the advances and achievements that have been made possible as a result of this funding."

Owens recited examples of what he called "the current biologic revolution" which is the result of funded research. "It is now becoming increasingly

clear that the support of Congress for funding of biomedical research is now permitting the outpouring of research findings at an ever increasing and unprecedented rate. It is also true that, almost without exception, the major advances in the treatment and cure of human cancers have resulted from carefully designed clinical trials, utilizing these findings. As you know, the majority of controlled clinical trials are conducted by the physician investigators in the nation's cancer centers and cooperative groups. It is the clinical oncologists, who have been trained in the design, conduct and evaluation of clinical trials, which constitute the nation's expertise and the application to cancer patients of the advances in laboratory research that may lead to the prevention, detection, treatment and cure of more human cancers."

Owens noted that the House Appropriations Committee last year asked for an NIH study of the patterns of clinical research since 1982. "A number of us are increasingly concerned that perhaps clinical research is not receiving the support that is required in order to translate the basic research findings into appropriate care as quickly as possible," Owens said.

"We recognize that appropriate funding levels for basic and clinical research are really a matter for NIH, NCI and the scientific community to determine from their experience; and the Congress, and especially the Appropriations Committees, have always made it a matter of policy not to interfere in these scientific decisions. We want to make it clear that we are not seeking congressional intervention in this matter, but are indicating that we are raising this as an issue that should be considered at this time by the scientific community.

"We are concerned, however, that the allocation of funds to support the NCI program of clinical research in cancer centers and by national cooperative groups has not kept pace with inflation nor has it kept pace with the opportunities now available to us."

Owens told Weicker, "We are deeply appreciative of the work of this committee and especially you in attempting to resolve the matter of the proposed cutback by the Office of Management & Budget of the levels proposed by this committee and Congress last year, of 6,500 grants to 5,000, for fiscal year 1985. These cutbacks will affect not only new research grants, but other programs, including cancer centers.

"We come before you as advocates of cancer patients, and of the research community which realizes the opportunities available. We are hopeful that, even in these stringent economic times, the NIH budget can be increased."

Owens summarized ASCO's recommendations:

"1. We urge that the bypass budget of $1.46 billion for NCI be adopted by Congress.

"2. We urge that the figure of $5.7 billion of the ad hoc group for Medical Research Funding also be agreed to by Congress for the entire NIH.

"3. We support the activities you and your subcommittee have taken in regard to resolving the fiscal year 1985 issues of the level of new research grants. We should also like to make the point that not only at issue are the number of research grants, but also the level of funding of cancer centers and of clinical research, which is intertwined with the larger issue of grants."

Murphy, who is director of Roswell Park Memorial Institute, referred to the American Cancer Society's requests in 1983 and 1984 for "the citizens' budget of $1.5 billion for the National Cancer Institute. The citizens' budget was based on what the Society determined would be the amount of funding that could be utilized effectively by the National Cancer Institute and maintain the dynamic momentum that had been achieved in the battle against cancer.

"The Society recognizes that in the current national economic crisis, it would be unrealistic to expect that a figure of $1.5 billion would be appropriated to NCI for FY '86. On the other hand, a national investment of $1.5 billion is needed to just maintain momentum that has been achieved.

"The American Cancer Society is not asking government to do it all. In a new departure for the Society, we are asking that Congress appropriate, and the White House approve, an FY '86 appropriation of $1.3 billion for the National Cancer Institute. At the same time, to achieve $1.5 billion in value of productivity in cancer research, the Society calls on the cancer research community—research institutions, investigators, suppliers, and others who impact on the cost of cancer research—to make a special commitment in FY '86 to tighten their belts, to do more with less, and accomplish $1.5 billion worth of cancer research with the $1.3 billion appropriation.

"Cancer research is expensive and Congress has consistently recognized over the years that high investment has yielded high returns," Murphy continued. "Cancer is an expensive disease. It is expensive because it is probably the most complex biological problem man has ever confronted. A study by the Blue Cross and Blue Shield Assn. showed that the average American who died of cancer in 1983 accrued more than $22,000 in medical expenses alone during the last yuear of life. Cancer, however, is a long struggle, and many patients require elaborate and costly treatment for several years. . .

"But cancer costs this country more than medical expenses. A person who is seriously ill with cancer is generally unable to work regularly and cannot contribute to the economy. Furthermore, federal, state and local governments cannot collect the same amount in taxes that the person paid when well and working full time. The National Center for Health Statistics found in 1980 that when lost wages and productivity were added to medical costs, cancer cost America $39.2 billion. Obviously, this total has risen during the five years since this study was performed.

"I have not touched upon the cost of cancer that cannot be measured in dollars. The physical toll upon the patient, his or her emotional suffering, the anxiety and disruption of the family—these are human costs of cancer that cannot be calculated... But my message to you is one of great hope. Our immediate concern is continued, adequate funding, not of a losing battle but of a dynamic national investment that is finally breaking down the seemingly impenetrable barriers that cancer used to represent."

Murphy added his list of the accomplishments made in cancer research to those of the other speakers, most of which, he said, "was underwritten directly or indirectly by the National Cancer Institute...

"The quality of cancer research is all important. As the individual responsible for a major basic and clinical research facility, I can assure you that cancer research can neither be done overnight nor undertaken in a day. Research is a continuum. Today's achievements grow out of yesterday's hard work which, in turn, evolved from the discoveries of the day before yesterday.

"Cancer research requires long term planning, dependable funding, and, perhaps most important, a cadre of well trained, intensely motivated scientists to do the work.

"The far sightedness of Congress in the past has provided the American cancer research effort with these crucial elements. As a result, this country unquestionably leads the world in cancer research. The great discoveries of the past decade, which may well lead to the conquest not only of cancer but of many other diseases, have all come from American laboratories, or have been based on the work of American investigators. . .

"The tradition of adequate funding, established by the National Cancer Act of 1971, has created a unique climate in which excellence has flourished. The intellectual excitement of fast moving cancer research has attracted the best and brightest of young scientists. The pace has quickened. The momentum of research has brought us to the brink of discoveries as profound as man has ever made.

"To interrupt this progress would be a national tragedy. Any reduction in the level of funding would be like throwing a boulder into the path of a marathon runner just before the finish line. To consolidate the success of recent years, applying it to people who have cancer today and people who will develop cancer tomorrow, it is vital that the federal government must continue to support cancer research at a level that will keep the life giving discoveries coming. Momentum of cancer research is a fragile commodity. It has been nurtured, cultivated carefully and firmly developed. The brightest minds have been encouraged to join the battle and have achieved a high pitch of productivity. But momentum remains volatile and depends on adequate funding. Any appropriation less than $1.3 billion would cause the momentum of research to dissipate and would waste much of the effort and investment of previous years.

"We have estimated that it would require $1.5 billion to maintain the present pace of research. We recognize, however, that American scientists, like all Americans, are threatened by the looming federal deficit. All of us, in our homes and our business, must try to economize wherever we can. The American Cancer Society therefore calls upon investigators, administrators, and everyone involved in the cancer control program to combine good citizenship with good science and to find prudent ways of spending a little less, and accomplishing more, to get a bigger bank out of the buck, so to speak.

"Where existing equipment can be repaired or updated, achieving the same results as an expensive new machine, we encourage investigators to make do with what they have. Without compromising quality, supplies should be bought from the most economical source. In the laboratory and at the bedside, just as at home and in the halls of government, small, common sense economies can add up to important savings.

"Thus, we believe the $1.5 billion worth of research needed to maintain the pace of excellence in the battle against cancer can, in fact, be achieved with a federal appropriation of $1.3 billion. I certainly intend to work towards that objective at my Institute."

Murphy and Owens managed to slip in pitches for renewal of the National Cancer Act.

"Although this is an appropriations hearing, I would like to note that the American Cancer Society believes that only if the $1.3 billion is properly administered can these savings be effected," Murphy said. "In our opinion, it is imperative for the present streamlined management structure of the National Cancer Institute to remain in place. This structure, which was built into the National Cancer Act of 1972, is responsible for much of the

outstanding cost effectiveness of the National Cancer Program in the past. Only with its modern, highly appropriate structure, can the National Cancer Institute be assured of the flexibility, autonomy, and the power to make scientific decisions based on the best scientific evidence. When the reauthorization of the National Cancer Act is brought up, we urge most strongly that it be passed.

"The National Cancer Program is one of the glories of the American people, and of our free democratic system. Through you and your colleagues, we have fostered a quality and a pace of cancer research that reflects their deep concern with this disease. We ask that you continue to act upon that concern and appropriate for the National Cancer Institute the $1.3 billion it needs for this urgent effort during the coming year."

Owens said, "Although this is not the committee concerned with the reauthorization of the National Cancer Act, as that is done by the authorizing committees of Congress, nevertheless I know that members of this committee have significant influence on the policies developed in the Senate in regard to biomedical research... I know that you feel as we do, that 14 years after the passage of the National Cancer Act, it should hardly be necessary to once again make the case regarding the remarkable forward progress, and the necessity of continuing the National Cancer Act as it was originally developed. It has proved to be an unarguable success."

NCI found out this week that it now stands a good chance of getting back the $4.3 million it would have lost through the rescision the Administration submitted to Congress. When Congress failed to approve the rescision request by the 45 day deadline, it was dead, but there was speculation that the White House would resubmit it.

However, OMB has informed NIH and NCI that the money will be available July 1. How it will be spent remains to be determined. NCI Director Vincent DeVita is out of the country, and Acting Director Jane Henney said the best guess might be returning it to the source—the areas from which it was cut, namely, consultant services, travel, printing. The final decision will have to await DeVita's return, and action by the NCI Executive Committee.

The NIH total involved in the rescision request was $10.45 million. The total for HHS was $26.8 million.

The money now apparently coming back to other major NIH institutes includes $1.4 million for the Heart, Lung & Blood Institute; $542,000 for Environmental Health Sciences; $1.17 for Arthritis, Diabetes & Digestive & Kidney Diseases.

FUNDS AVAILABLE FOR COLLABORATIVE RESEARCH IN FRENCH, ITALIAN LABS

U.S. scientists have not been taking advantage as much as they might of opportunities to work in France and Italy for periods up to one year, expenses paid, under bilateral agreements between NCI and those countries.

NCI, the French Institut Nationale de la Sante et de la Research Medicale (INSERM), and the National Cancer Institute of Milan jointly sponsor cooperation in basic and clinical cancer research. Funds are available in this program to provide travel expenses and subsistence allowances for U.S. scientists to work in France and Italy for periods of three weeks to one year on collaborative research projects with their European colleagues.

Each request for support will be reviewed for scientific merit by the international program committee. Applications should include a short summary of the research to be supported, letter of invitation from the European sponsor, and the proposed itinerary. The deadline for applications is June 1, and applicants will learn of the committee's decisions by July 1.

For further information, contact Dr. Gregory Curt, Deputy Director, Div. of Cancer Treatment, Bldg 31 Rm 3A51, Bethesda 20205.

PHS REVISES POLICIES ON CARE, USE OF LABORATORY ANIMALS IN RESEARCH

The Public Health Service has revised its policy on the humane care and use of laboratory animals, NIH has announced. The new policy tightens and expands requirements.

There are five major areas of change in the revised policy:

1. Institutions are required to designate clear lines of authority and responsibility for those involved in animal care and use in PHS-supported projects. Each institution must identify an official who is ultimately responsible for the institution's animal program and a veterinarian qualified in laboratory animal medicine who will participate in the program.

2. The policy upgrades the role and responsibilities of animal care and use committees of local institutions and their involvement in all aspects of the instution's PHS supported animal research program. The policy requires that the use committee include an individual unaffiliated with the institution, a veterinarian with training or experience in the care and use of laboratory animals, a practicing scientists experienced in research involving animals, and a member whose primary concerns are in a nonscientific area.

3. The policy mandates each institution to

provide detailed information regarding the institution's program for the care and use of research animals in PHS-supported activities. The additional information will aid in the assessment of each institution's commitment to animal welfare and its ability to comply with the policy.

4. The policy requires institutional animal care and use committees to review and approve those sections of research applications for PHS funding that relate to the care and use of animals. The PHS will not award funds for research involving animals until the approval is documented.

5. Any institution that is not accredited by the American Assn. for Accrediation of Laboratory Animal Care—the recognized nongovernmental accrediting organization in the field—will be required to conduct a self assessment of its animal research program based on the "NIH Guide for the Care and Use of Laboratory Animals." Deficiencies in an institution's program or facilities must be reported to NIH and the institution must adhere to an approved time frame for the correction of the deficiencies. An updated version of this guide, prepared by the Institute for Laboratory Animal Resources within the National Academy of Sciences, will be released shortly.

NTP STAFF IMPLEMENTING 95 PER CENT OF AD HOC PANEL RECOMMENDATIONS

National Toxicology Program staff has already implemented or is in the process of implementing more than 95 per cent of the recommendations made last year by the Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation, NTP Director David Rall said last week.

The NTP Board of Scientific Counselors heard a report on the staff's responses to the recommendations which, for the most part, agreed with the Panel. In some cases the responses explained what was being done to implement the suggestions; in a few instances, the responses explained why it was not feasible or desirable to comply.

A report on the Panel's recommendations appeared in **The Cancer Letter** Sept. 7, 1984.

John Doull, professor of pharmacology and toxicology at the Univ. of Kansas Medical Center who chaired the Panel, said the group felt that its work and report was "a substantial first step, but only a first step. We hope that NTP will pursue further, through workshops, areas we didn't give definitive answers to."

BSC Chairman Mortimer Mendelsohn agreed that "we must go on with this process." Rall pointed out that "this is an ad hoc process, and the next panel might be quite different. I think that about every five years we should take a quick look at what problems are developing and create a new panel to deal with them."

Mendelsohn said that five years "may be too long to wait," and Rall agreed.

Norton Nelson, who was chairman of the NTP Board when the Panel was established and given its charge in 1983, said, "I was a little nervous about this at the start. An awful lot rests on this, in the eyes of the nation and the world. It involves some quite diverse and sometimes violent opinions. In my secret heart I thought that a great, brilliant stroke would come out that would simplify the whole thing. It didn't, but maybe next time. The old pattern has been very much improved, but it still relies on old ways. That leaves me with some disappointment. However, I am encouraged."

NTP BOARD APPROVES CONCEPT FOR NEW IN VITRO STUDY WITH USE OF ONCOGENES

The National Toxicology Program Board of Scientific Counselors approved the concept last week for a three year cooperative agreement to support a study for in vitro transformation of oncogene primed cells by genotoxic chemicals. Staff estimated the total cost at $465,000. Raymond Tennant of the Cellular & Genetic Toxicology Branch said he would like to fund two separate labs for the study, "but the budget probably will limit it to one."

The Board rejected a concept for a joint effort with the Environmental Protection Agency for a retrospective study of premanufacture notification health hazard predictions. The study would have looked at the results of EPA's use of structure activity relationships to evaluate the potential hazards of new compounds and determine through a batter of tests how well SAR had done.

"The intent of the study would be to determine of structural activity relationships works in predicting hazards," William Farland of EPA said. "If it doesn't, we would go to Congress and ask for legislative changes."

Farland explained that the Toxic Substances Control Act does not require manufacturers to conduct toxicity testing on chemicals prior to submission of premarket notification. "The task before EPA is to determine, despite a paucity (often an absence) of test data, whether the chemical under its projected conditions of manufacturing, processing, use, and display may or will present an unreasonable risk of injury to human health or the environment."

Structural activity relationships (SAR) analyses involve review of submitted test data, if any; review of test data available on analogous substances; and the professional judgments of scientific assessors in interpreting and integrating that information. EPA's use of SAR has been the subject of criticism from Congress, environmental groups and

others who point out the uncertainties associated with that approach.

Norton Nelson, former chairman of the NTP Board, said that TSCA "is a lousy law, but I find it distasteful to try to prove SAR doesn't work in order to change the law." Nelson also has been chairman of EPA's Science Advisory Board.

NTP Board member Jerry Hook said, "NTP is being set up to fail. I don't think we should allow that."

Responding to NTP Board member Norman Breslow's question on what would constitute an unacceptable level of association between SAR predictions and hazards eventually seen, Farland said, "If it is 50 per cent, we're not benefitting from the tools available. But I don't share the view that we are destined to find SAR doesn't work."

"I agree that 50 per cent is unacceptable," Breslow said. "That's no better than flipping a coin."

Board Chairman Mortimer Mendelsohn added, "It's an inadequate testing procedure, with inadequate sampling. It's doomed to failure. We want to help, but this is not the way to do it."

NTP Director David Rall suggested that the study might look at fewer compounds more intensively, with a broader battery than proposed in the concept. Board member James Swenberg suggested that the SAR system could be applied to the big NTP data base, using the chemicals already tested. "That would conserve animals and money and give you the answer you want."

When Rall summarized, "The Board accepts the need for a study, but rejects the concept as presented," the Board unanimously agreed.

Staff description of the concept for in vitro transformation of oncogene primed cells by genotoxic chemicals follows, with some editing to conserve space:

Based on the concepts of oncogene complementation and multistep carcinogenesis, we proposed to study in vitro transformation induced by genotoxic chemicals in cells that are engineered to inappropriately express cellular oncogenes. By specifically activating certain oncogenes that are insufficient to fully transform cells, preneoplastic phenotypes may be created that are more clearly defined and are more experimentally manipulable than any that currently exist in culture. Such target cells would then be further transformed by chemically induced genotoxic events, possibly including the activation of other oncogenes. The critical genetic target for transformation might be expected to vary depending on which oncogene is experimentally activated. We propose the development of proto-oncogene expression clones (recombinant DNA) and an extensive analysis of the phenotype of a variety of recipient cells. An investigation into the possibility of distinguishing chemicals based on their ability to induce genotoxic effects that readily transform cells that express some, but perhaps not other, proto-oncogene recombinant constructs is also proposed.

We propose an investigation into the possibility that genotoxic effects that result in the transformation of such oncogene primed cells can be transmitted by DNA mediated transformation (transfection). Of particular interest is the possibility that transfection of certain recipient cells requires complementation by the same oncogene as used in the original primed target cell. This may prove to be a valuable approach for identifying critical genetic targets that contribute to neoplastic transformation.

The value of developing and studying this system will be to increase our basic understanding of the role of certain oncogenes and their interaction with other genetic targets in neoplastic transformation. Cell lines developed in this research may prove to be very useful targets in routine in vitro assay systems. In addition, certain oncogene primed cell lines may prove to be sensitive to transfection by classes of oncogenes that are not detected by the standard NIH-3T3 transfection assay.

Initial work will focus on activation of proto-oncogenes by inappropriate expression rather than somatic mutation in protein coding sequence. For example, the proto-oncogene c-myc might be cloned into retrovirus vector. This would allow the gene to be efficiently introduced into cells in culture and be expressed at levels regulated by the viral LTR. The first phase of this might then be to infect primary cultures and cell lines of several rodent species and possibly human cells with the retrovirus/c-myc construct (helper virus free). These cells and cell lines would be characterized with respect to parameters important to in vitro cell transformation such as serum requirement, morphology, anchorage independent growth, immortality (for primary and low passage cell cultures) tumorigenicity, and stability of these properties. Based on these findings, target cells, appropriate measurement endpoints and appropriate controls might be selected to evaluate transformation by genotoxic chemicals.

How a particular in vitro property that is used as an endpoint (morphology, growth in soft agar, focus formation, etc.) correlates with discrete stages of tumorigenesis or essential properties of tumor cells is very important. A detailed characterization of the phenotypic properties of different cell types expressing cloned c-onc genes and those subsequently transformed by chemical treatment may yield a better understanding of these issues.

The conceptual framework for this project is a hypothesized cooperation between the activated c-myc gene (or other c-onc to be used) and some chemically induced genetic effect, neither of which alone would cause transformation. Although initiation/promotion/progression imply a temporal relationship, the concept of a multistep mechanism of carcinogenesis may not necessarily require an ordered sequence of events. Events thought to occur early or late in progression to neoplastic transformation might be mimicked by manipulating the right c-onc genes.

A significant increase in the transformation frequency induced by a given chemical in engineered

oncogene expressing cells, relative to primary cells or an appropriate control cell line, would suggest that the oncogene or resulting phenotype was complemented by the chemically induced genotoxic event. If preliminary work supports the hypothesis that certain oncogene primed cells are readily transformed by some genotoxic chemicals, including rodent carcinogens, the future research possibilities are very broad. In addition to attempting to distinguish among chemicals and oncogenes by their ability to establish an efficient transformation system, a very interesting area of investigation relates to identifying critical genetic targets of the genotoxic chemicals. For example, transfection of the DNA from transformed cells into NIH-3T3 cells as well as oncogene primed cells could lead to the identification of additional genes involved in transformation.

Since transformation is the closest in vitro surrogate for carcinogenesis, research efforts should continue to be focused on improving the measurement of this phenomenon. Modifying complex cellular interactions by manipulating the expression of cloned genes offers new possibilities for selecting the phenotypic substrate upon which genotoxic/carcinogenic events can be measured.

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-CM-57705-16

Title: Surveillance and selection of natural products

Deadline: Approximately July 1

One cost type contract is expected to be awarded to a contractor with the capability to conduct a surveillance of currently published literature in the natural products area. The objective is to select the names and structures of new and novel compounds, especially those exhibiting biological activities, i.e., antitumor activity, cytotoxicity, antiviral activity, etc., for the purpose of acquisition of compounds of potential antitumor activity. Surveillance is to cover at least 150 journals in the natural products and related fields.

The findings are to be reported every two months in the form of (a) copies of the original articles (or abstracts if the original articles are not available); (b) summary of the following information in a booklet form: name of compound, structure, class of compound to which the product belongs, biological activities, isolated quantities, source; and (c) an alphabetical listing of the new compounds selected.

Interested offerors must demonstrate the following:

1. A proposed team with the following qualifications:

A. The principal investigator should have a degree at the PhD level in organic, medicinal or natural products chemistry, or a closely related discipline, and must have a strong background in, and recent experience with, natural products structures and chemical searches, as well as having background and experience with biological activity, preferably in the cancer area. The Natural Products Program requires the PI to have in depth knowledge of the natural products area and ready familiarity with organic and medicinal chemistry for the selection of articles and chemical structures of probable interest to the project. The contract will not involve a simple retrieval of articles published, but a selective retrieval, requiring the ability of the PI to recognize natural products compounds that could be of biological interest to the program.

B. Staff--the staff members to be used on the project should have a degree at the bachelors level in either chemistry or library science.

2. Awareness of the type and comprehensiveness of the searches and literature data to be submitted. The ability to obtain data in a timely fashion is essential, as is knowledge of the appropriateness of journals to be searched, proposed search methods, and the format of the output.

3. Availability of adequate facilities and equipment:

A. Library—ready access to a large library with extensive holdings in the areas of biology, chemistry, microbiology, pharmacology, biochemistry and medicine is required for the project.

B. Other--adequate space for offices, filing, record keeping, etc., should be available.

4. Appropriateness of organizational qualifications in the field of literature surveillance and availability of consultation and support to this project.

The contract period will be three years, beginning approximately Jan. 27, 1986.

The concept from which this RFP was derived was approved by the Div. of Cancer Treatment Board of Scientific Counselors last fall and was reported in The Cancer Letter Oct. 26, page 3.

Contract Specialist: Patricia Shifflett
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