THE CANCER LETTER

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INTERIM FUNDING: NONCOMPETING RENEWALS REDUCED BY 4 PERCENT, COMPETING CURRENT PLUS 7 PERCENT

NIH and NCI reached some conclusions this week, subject to change, on how 1982 fiscal year funds will be distributed in light of the continuing resolution approved last month by Congress and the President which provides interim financing through March.

HHS agencies will be permitted to spend at a level four percent under amounts included in the appropriations bill approved by the House, under terms of the continuing resolution. The House figure for NCI is $1.030 billion ($1 billion, 30 million). The four percent reduction brings that down to $989 million, almost identical to the total appropriated for NCI in the 1981 fiscal year. That amount includes $47.9 million for the National Toxicology Program.

That will not necessarily be the total amount NCI will get in the

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In Brief

GAO SAYS CONGRESS SHOULD RE-EXAMINE DELANEY CLAUSE, CONSIDER MAKING IT MORE FLEXIBLE

GENERAL ACCOUNTING OFFICE, in a report titled "Regulation of Cancer-Causing Food Additives—Time for a Change?", suggests that "Congress should re-examine whether the Delaney Clause is still appropriate because of (1) advances in the ability of analytical detection methods to identify substances at very low levels, (2) uncertainties about the human risk from low levels of carcinogens, and (3) the inflexibility of the current law. . . . The Delaney Clause is a source of controversy, an emotional issue, and a target for change." Delaney requires FDA to prohibit food additives which have been found to induce cancer when ingested by humans or animals. Congress has legislated an exception for saccharin, and Sen. Orrin Hatch (R.-Utah) has introduced a bill which would make the law more flexible and which is being opposed by some public interest groups. The GAO report, HRD-82-3, dated Dec. 11, 1981, may be requested free from U.S. GAO, Document Handling & Information Services Facility, P.O. Box 6015, Gaithersburg, Md. 20760, phone 202-275-6241. . . . NCI DIRECTOR Vincent DeVita, commenting on last year's investigations and media reports: "If you add up everything, press coverage overall has been fair and accurate. NCI is the most scrutinized agency in government. We've been looked at upside down, head to toe, and sideways. We've come out pretty well, I think." . . . CORRECTION: The listing of the meeting of the Div. of Cancer Cause & Prevention Board of Scientific Counselors Feb. 25-26 (*The Cancer Letter*, Jan. 1) indicated that it will be open both days. The meeting will be closed Feb. 25 when the Board will review various aspects of the DCCP intramural program.

PRESIDENT'S FY 1983 REQUEST FOR NCI WILL BE $950 MILLION, WITHOUT NTP

(Continued from page 1)

1982 fiscal year. The Senate Appropriations Committee has approved $1.034 billion for NCI, and action by the full Senate is expected soon after Congress reconvenes later this month. Assuming that a regular appropriations bill can be passed without a Presidential veto, NCI might well receive an additional $40-45 million.

Until then, however, the four percent reduction will be applied in this manner, NCI executives tentatively decided at a meeting Tuesday:

- Noncompeting grants will be renegotiated with funding to be reduced by four percent, instead of the 12 percent announced by NIH in December when the White House was trying to get Congress to cut appropriations by that amount.
- New grants may be awarded, as long as they can be worked into the overall budget. The December order had precluded award of all new grants. Some new awards may be deferred until later in the year. Some reductions may be made, in most cases probably will be made, from recommended levels.
- Competing renewals, including cooperative group and cancer center core grants, will be funded either at the recommended levels or the current levels plus seven percent, whichever is lower.
- The sliding scale method of funding center core grants, with the highest scoring grants funded closer to recommended levels, will be held in abeyance until the final budget picture becomes clear.
- Training grants will suffer the same reductions applied to R01s, that is four percent. Awards involving essentially salary only, such as research career development, will be made without reduction.

The 1983 fiscal year budget is in the final stages of development by the White House, with its request scheduled to go to Congress in late January or early February. The Presidential budget request for NCI will be about $950 million, not including NTP funds which have been transferred to the National Institute of Environmental Health Sciences budget. That would represent an increase of less than $10 million over the $941.1 million the Administration wants to hold NCI to in the current fiscal year, but more than $150 million under the National Cancer Advisory Board's request in the bypass budget.

If Congress appropriates $40 million more in 1982 than requested by the White House, it is not likely to take it back in 1983. It appears that NCI's budget in 1983, without NTP, finally could hit the $1 billion mark.

CALGB GRANT APPROVED, BUT THE GROUP MAY LOSE ITS NON-HEMATOLOGIC STUDIES

The Cancer Clinical Investigation Review Committee has approved renewal of the Cancer & Leukemia Group B grant on a split vote, but the group—one of three original cooperative groups—stands to lose a major share of its NCI support.

The CCIRC review in general was favorable toward CALGB's leukemia and lymphoma studies but negative toward much of its non-hematologic activities. In previous years, NCI probably would have continued full support of the group while urging that efforts be made to improve the weaker areas. However, facing their most severe budget crunch since 1971, NCI executives are seriously considering eliminating or phasing out support for CALGB's non-hematologic studies.

CALGB Chairman Emil Frei and members of his executive committee were scheduled to meet this week with NCI executives to discuss the situation.

Phasing out of all but the leukemia and lymphoma studies would be the second major reduction in CALGB activities within the last two years. The group's pediatric segment pulled out and formed the new Pediatric Oncology Group, with Teresa Vietti as chairman.

CALGB was established in 1955 as Acute Leukemia Group B to develop clinical trials for treatment of the disease in adults. Acute Leukemia Group A did the same with childhood leukemia. Group A's activities eventually were absorbed by other groups, and Group B developed its own pediatric segment which is now POG.

AGING INSTITUTE ENCOURAGES CANCER INVESTIGATORS TO INCLUDE ELDERLY

The National Institute on Aging is encouraging cancer investigators to add some elderly patients to their clinical protocols and is offering support through two NIA grant programs.

"A major problem relates to the fact that drugs used in the elderly have been tested in young adults, not in the elderly themselves," said George Steinberg, who is with NIA's Pharmacology Program. "There have been numerous reports of increased incidence of side effects in the elderly. We do not know whether, in fact, the reported increases are real, or, if real, whether the increases are due simply to inappropriate dosage for this population or to more fundamental differences in pharmacodynamics."

Anticancer chemotherapy protocols usually exclude patients over age 75, sometimes those over 65. Investigators are concerned about the ability of older persons to tolerate cytotoxic agents, and they like to have a patient base young enough to assure long term followup.

One NIA grant program is intended to provide small awards for pilot projects, a maximum of $15,000 in direct costs for technical assistance, supplies, small equipment and travel. A program announcement was issued last year, and the application receipt date is Feb. 1, 1982.

Among the categories of research this program will support was pharmacology—clinical and basic studies aimed at understanding the pharmacodynamics and pharmacokinetics of drugs on the central and peripheral nervous systems and the cardiovascular system; and clinical investigations of drug interactions.

A new program announcement is being prepared which will state NIA's interest in clinical and basic research to gain fundamental knowledge on how and why the elderly differ from young adults in their response to drugs. This program will support both research projects and research training.

A draft of the new program announcement cites specific ojbectives:

"NIA seeks research and research training grant applications in gerontological and geriatric pharmacology. Investigations are encouraged on the aging process (beyond maturity) in all of the physiological systems that are subject to pharmacological intervention. Among possible approaches are clinical studies of healthy and diseased elderly persons and more basic studies in experimental animals. Appropriate topics include but are not limited to the areas noted below. These areas are not listed in any order of priority.

"Areas of greatest needs or opportunities—General: Drug actions on the peripheral and central nervous systems, and on the cardiovascular system. Effects of drugs and modulators on the immune system and on bone metabolism. Specific problems or conditions: dementias, osteoporosis, decubitus ulcers, arthritis, incontinence, and infection.

"Basic pharmacology—Basic and clinical pharmacological research which leads to increasing fundamental knowledge on how and why the elderly differ from younger people in their response to drugs. Emphasis on research having a pharmacodynamic basis is encouraged. Studies of the pharmacokinetic behavior of drugs is encouraged only where there are direct and clear relationships to problems of drug action or to important physiological or homeostatic processes.

"Clinical studies—Evaluation of individual drugs to provide definitive guidance for their use in the elderly. Information to be obtained should include: proper dosage levels, effectiveness, side effects, interactions with other drugs, interactions with other disease states, nutritional status, etc."

"While neither explicitly includes cancer studies, such studies certainly will be welcome under either," Steinberg said.

The standard research grant application form PHS 398 should be used for the project grants, and form PHS 6025 for training grants. Inquiries and correspondence should be directed to George Steinberg, PhD, Pharmacology Program, Bldg 31 Rm 5C-23, NIA, NIH, Bethesda, Md. 20205, phone 301-496-1033.

BRMP INVESTIGATORS FIND NEW HUMAN LUNG TUMOR ANTIGEN, SEEK DEVELOPERS

Investigators in the Biological Development Branch of NCI's Biological Response Modifiers Program have isolated a new human lung tumor antigen which may be useful as a marker.

James Braatz, senior investigator for the group, said that the antigen appears to be present in generally higher levels in the sera of untreated lung cancer patients relative to sera from normal individuals and patients with benign lung disease.

Braatz and his colleagues hope to find companies willing to commit research facilities, personnel and other expenses to the development of an assay kit and to fully evaluate the clinical usefulness of the marker. No government funds are available to support the development.

An account of the work has been accepted for publication, and preprints are available upon request. A patent application has been submitted.

For preprint copies and other information, contact Braatz at NCI, Frederick Cancer Research Facility, Bldg 560 Rm 31-93, Frederick, Md. 21701, phone 301-663-2923.

U.S.-GREAT BRITAIN SUMMIT CONFERENCE REVIEWS LEADS IN LEUKEMIA, LYMPHOMA

The first scientific summit conference by the United States and Great Brain, at Leeds Castle, in Kent, discussed the most promising leads in research on leukemias and lymphomas and ways to intensify collaborative research between scientists in the two countries.

The meeting resulted in a review of significant research results from scientific disciplines as varied as medicine, genetics, and the rapidly advancing fields of cellular and molecular biology. The following perspectives emerged:

- Specific changes in cell chromosomes are a reliable indicator of cancer for chronic myelocytic leukemia, acute myelogenous leukemia, acute promyelocytic leukemia, and Burkitt's lymphoma, and are suggestive of leukemia or lymphoma in patients with an hereditary muscular disorder, ataxia telangiectasia, who have an increased risk of cancer.
- Scientists can now isolate human chromosomes and order their genes. It now appears possible that they soon will be able to identify the molecular sites of specific translocations (from the normal site on the chromosome to a new site on the same or another

chromosome). In coming years, research in molecular biology is expected to identify more closely the molecular abnormality that is leukemia.

- Each patient with leukemia or lymphoma has many abnormal cells circulating in his blood or lymph system; only a small percentage of these cells may give rise to new cancer cells. Treatment might be improved by finding ways to direct drugs against the true immortal cells.
- No two leukemic patients appear to have the same marker antigens on the leukemic cells, or the same requirements for growth of their cells in laboratory cultures.
- Defects of DNA repair have been identified in Downs' and Bloom's syndromes and in Fanconi's anemia. Patients with these hereditary conditions have an increased risk of leukemia or lymphoma, as do patients with certain types of immune system disturbances.
- Drug resistance is a major cause of treatment failure. A new mathematical model to explain the rate of development of drug-resistant cancer cells has been published. The model has stimulated studies of alternating, non-overlapping drug regimens that can kill cancer cells before they develop resistance.
- A number of chemicals, such as alkylating agents, are very effective in treating existing cancer, but also increase surviving patients' risk of developing leukemia.
- Because of the risk of medical complications following bone marrow transplantation, this infrequently used treatment is expected to have even more limited applications as less toxic therapies are developed.
- Animal studies suggest that it may be possible to develop drugs that will help leukemic cells return to a normal appearance and function. (It is far too early to know whether such drugs will ever supplant conventional drug therapy.)

In a message to conference participants, President Ronald Reagan said, "...This joint endeavor represents an extraordinary effort by a dedicated group of experts from both countries to address the complex issues confronting current research in leukemia. As one of the most common forms of cancer striking young children, leukemia is a particularly heart-rending disease. All progress in treating this illness represents a major contribution to the humanitarian concern and well being of all people. . . ."

The conference participants discussed possible U.S.-Great Britain collaborative projects, including studies of a unique virus isolated in the United States from a human T-cell lymphoma by Robert Gallo and his coworkers at NCI. A similar, if not identical, virus was isolated again in Japan recently, where leukemias and lymphomas of mature T-cells are more common than in the United States.

On the molecular level, there is now clear evidence from animal models that a virus that causes leukemia after a long latent period does so by activating certain cellular genes. Participants discussed the implications of these findings for other forms of cancer, and agreed that the eventual merger of chromosomal and molecular studies will provide insights into the causes of cancer.

Another important model for human cancer, discussed at Leeds Castle, is the Epstein-Barr virus, which causes leukemias and lymphomas in subhuman primates. This herpesvirus is associated with Burkitt's lymphoma and with a very rare, acute lymphoproliferative disease in children.

Cochairmen of the conference were John Dacie, chairman of the Medical and Scientific Advisory Panel of the Leukaemia Research Fund of Great Britain, and Henry Kaplan, Stanford Univ. Medical Center.

Participants agreed to meet in the United States one year from now to examine progress in cellular and molecular research.

CHANGES IN CANCER CELL BEHAVIOR NOTED AT BRISTOL-MYERS SYMPOSIUM

Data on striking changes in the behavior of human cancer cells emerged in 28 papers presented during the fourth annual Bristol-Myers Symposium on Cancer Research at Johns Hopkins last month.

Four hundred scientists from the U.S. and abroad attended the two-day meeting on tumor cell heterogeneity, which was organized by Albert Owens Jr., director of the Johns Hopkins Oncology Center.

Paul Calabresi, chairman of the department of medicine at Brown Univ., reported that clinical experience with colon cancer patients points to the existence of tumor cell heterogeneity—a single tumor may contain more than one kind of cancer cell.

Viewed under a microscope, he said, one patient's tumor showed two groups of cancer cells. One group contained the normal number of chromosomes; the other contained almost double that number. One group grew readily in a laboratory culture; the other did not. One group produced considerable carcinoembryonic antigen (CEA); the other produced almost none.

This tumor cell heterogeneity casts doubt on the effectiveness of monitoring for recurrence of colon cancer after surgery by screening for CEA, Calabresi observed. It also compromises the validity of testing drugs on patients' cancer cells grown in vitro, he said.

The instability of the genes and chromosomes in cancer cells was a recurrent theme of the symposium. Avery Sandberg, chief of genetics and endocrinology at Roswell Park Memorial Institute, said that gross chromosomal changes can be seen in virtually every

type of cancer cell.

Differences in cancer cell sensitivity to immune attack were cited by Isaiah Fidler, Frederick Cancer Research Facility. Evidently, the spread of cancer from the initially invaded tissue to other parts of the body (metastasis) that is responsible for the death of most cancer patients depends on genetic changes which permit growth in a new environment.

George Todaro, NCI, presented evidence that some cancer cells are capable of "turning themselves on" by producing growth factors for which they have receptors. Ordinarily in the body, one group of cells produces a hormone or other messenger that tells cells of another gland, organ or tissue what to do. Todaro said he has found, however, that certain cancer cells can both send and receive the same message, namely, one that spurs cell replication.

Reporting on studies of lymphatic cancer in mice, Garth Nicholson, M.D. Anderson Hospital & Tumor Institute, said he found that a subpopulation of tumor cells with certain markers (antigens) on their surfaces were best able to metastasize. Nicholson said he was thus able to identify which cells were more lethal. This form of heterogeneity in cancer cells might be used to stimulate an immune attack directed against those markers, Nicholson suggested.

The activation of a gene present in the chromosomes of birds, mammals and man has been linked for the first time with some forms of human leukemia and lymphoma, Susan Astrin, Fox Chase Cancer Center, reported.

Astrin said that she and William Hayward, of Rockefeller Univ., have found evidence of a gene, scientifically labeled Myc, that is expressed, or turned on, inappropriately. The Myc gene appeared in the white blood cells of five out of six leukemia and lymphoma patients tested, but not in normal white blood cells of eight volunteers.

A number of animal cancers are now known to start when different tumor viruses turn on genes—such as Myc—called "oncogenes." Astrin said it appears that oncogenes carry the genetic code instructions for substances that the body normally makes in its development from fertilized egg to mature adult.

She speculated that the Myc gene could produce a "messenger chemical" that instructs cells to proliferate or differentiate (change their functions) during fetal life. Since the Myc gene has been conserved through the evolution of birds and mammals, including man, it is apparently an important genetic unit, she said.

Astrin first studied a tumor produced in chickens when fertile eggs were infected with avian leukosis virus. The chickens developed cancer of the bursa, an organ whose cells function much like the immune white cells of humans—the cells involved in leukemias and lymphomas. Some of the genetic material of the virus showed up in the bursa tumor cells. Moreover, according to Astrin, the cells actively transcribed the message coded on their Myc gene.

Since the Myc gene in chickens is virtually identical to the Myc gene in man, Astrin sought evidence of the gene's activity in cancerous white blood cells of patients with acute lymphatic leukemia (ALL) or lymphoma. She and her colleagues found that the gene was inactive, or repressed, in normal cells, but actively sending messages in the cancer cells of two of the three lymphoma patients and all three ALL patients.

Furthermore, she reported that when drug treatment had returned the blood of one leukemia patient to normal, the Myc gene was no longer active in the white cells.

Astrin stressed that her work does not "prove" that viruses cause either lymphoma or leukemia. Indeed, she did not seek or find evidence of a viral cause.

Earlier in the session, Bernard Weinstein, professor of medicine and environmental sciences at Columbia Univ.'s College of Physicians & Surgeons, New York, presented evidence that cancers in mice caused by chemical compounds also showed signs of having oncogenes.

Thus, investigation of the functions and products of oncogenes may be relevant to many cancers, regardless of their origins. While the avian leukosis virus has been known for more than 25 years, techniques for locating specific oncogenes have become available only in the last few years.

A strain of prostate cancer, transferred to rats and continually grown for more than five years, is helping medical scientists to understand why most men with this form of cancer at first respond to treatment but later relapse.

John Isaacs reported on the usefulness of rat prostate cancer in studying human disease. He is assistant professor of oncology and urology at Johns Hopkins Univ. School of Medicine. He has found that after varying periods of growth in animal hosts, prostate cancer cells multiply more rapidly, and the number and appearance of their chromosomes change dramatically. These changes, he said, make the cells much more lethal to rats.

Behind Isaacs' research lies the question of how and when to attack genital cancer in men with maximum impact. Castration has been the main form of therapy for many years, usually accompanied by radiation when the cancer has spread beyond the gland.

Isaacs said that removal of the major source of the male hormone, testosterone, temporarily halts

the growth of the cancer, or often even shrinks the tumor, in four out of five patients. It's evident, he said, that most of these tumor cells require the hormone to thrive. In time, however, cancer cells that don't require testosterone invariably resume the attack.

Do the six-hormone-independent cells appear during treatment or are they present from the beginning? The answer to that question is vital to attempts to devise better treatments for the cancer. From his study of the tumor cells in rats, Isaacs reported that the hormone-independent tumor cells seem to be present almost from the start, even before any cancer symptoms appear.

These findings suggest that hormonal treatments alone can't cure prostate cancer in rats or in man—even though they can produce very substantial temporary remissions. The hormone-independent cells, present from the beginning, are the reason for the ultimate failure.

RFPs AVAILABLE

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

RFP NCI-CM-37537

Title: *Operation of a rodent serological virus surveillance laboratory*

Deadline: *April 12*

The Animal Genetic & Production Branch, Developmental Therapeutics Program, Div. of Cancer Treatment, NCI, is seeking proposals from qualified organizations having the capabilities, resources, and facilities for the operation of a rodent serological virus surveillance laboratory.

Purpose of this project will be to operate and maintain a virus serum diagnostic laboratory. Serum samples will be submitted from contract rodent suppliers and testing laboratories on a schedule provided by the project officer. A total of approximately 40,200 virus tests will be performed annually. Profile of testing results will include four to nine viruses depending upon the animal being tested.

Rodents to be tested will include mice, rats, hamsters, and guinea pigs. This project requires extensive guidance by the project officer including scheduling of submission and monitoring of results with an absolute requirement for a very short turn around time for submission of material to reporting of results.

It is anticipated that the award will be a negotiated fixed price contract for a period of one year with an option to extend the contract on a yearly basis for four additional years. Important factors in the selection process will include the experience and expertise of the principal investigator in the area of rodent viral surveillance, demonstrated experience of staff members, demonstrated organizational experience and expertise in requirements of this project along with acceptability of proposed methods and facilities and equipment available for operation of the laboratory.

Contract Specialist: Marlene Haywood
RCB, Blair Bldg. Rm. 228
301-427-8737

RFP N01-CP-26505-74

Title: *Hamster respiratory carcinogenesis resource for in vivo/in vitro correlation studies*

Deadline: *Feb. 22*

A resource is sought to provide good facilities and competent personnel to perform the following work: a) maintenance and treatment of hamsters with various carcinogens and co-factors, alone or in combination; specialized treatment methods include intratracheal instillation of carcinogens carried by particulates in suspension, as well as systematic administration; b) necropsy of experimental animals and tissue pathology examination, with special fixation procedures for respiratory organs, embedding and sectioning of larynx, trachea, bronchial tree and other organs as needed; c) preparation of selected tissues by specialized techniques, e.g. histochemistry and E.M.; particularly including histochemical markers of respiratory epithelial differentiation; and d) tissue explants for preparation of organ and cell cultures including preparation of tissue explant cultures for transplant to LEP, and longer term cultures for respiratory epithelial tissues and cells. It is expected that no more than 2,000 hamsters/year will be needed, while animal maintenance costs will average 700 animal-years.

Organizations submitting proposals must have (or be willing to establish prior to contract award) facilities within a 60 mile radius of the Frederick Cancer Research Facility, Frederick, Md.

Contract Specialist: Odessa Henderson
RCB, Blair Bldg.. Rm. 2A07
301-427-8771

The Cancer Letter _Editor Jerry D. Boyd

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