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NCI Stands Firm On ASSIST 'Downscaling' Despite 150 Letters From States, Volunteers

NCI executives are standing firm on their decision to provide less money this year than had been planned for the Institute's multi-million dollar smoking intervention study.

However, NCI is looking at adding another year to the seven-year study. The Institute has said it will provide $18.2 million this year for the American Stop Smoking Intervention Study, $5.1 million less than

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In Brief

ASCO Letter To Clinton Urges Support For Trials; Senator Praises NCI, Bristol; Berlin Back At NCI

HEALTH CARE REFORM should include reimbursement for care provided in clinical trials, American Society of Clinical Oncology wrote to the Transition Office of President-elect **Bill Clinton**. "It is critical that any health care reform proposed by the new Administration include, as part of any minimum benefits requirement, provision for reimbursement in connection with care provided in clinical trials," ASCO wrote. "By doing so, a reformed health care system can encourage advances in medicine while also providing optimal care for desperately ill patients, regardless of their ability to pay." . . . **SEN. BENNET JOHNSON** (D-LA), in a letter to NIH Director **Bernadine Healy**, commended NCI and Bristol-Myers Squibb on the development of taxol. "In less than two years, Bristol-Myers Squibb collected almost four times the amount of [yew] bark than had been collected over the previous 10 years, embarked on a 'Manhattan-type' project to find an alternative source, and filed and successfully obtained approval of an NDA for Taxol," Johnson wrote. . . **NATHANIEL BERLIN**, former director of NCI's Div. of Cancer Biology & Diagnosis, has returned to NCI for a year to work with his successor, **Alan Rabson**. Berlin left NCI in 1975; since 1987 he has been deputy director of the Univ. of Miami's Sylvester Comprehensive Cancer Center. "I'm not doing anything operational," Berlin told **The Cancer Letter**. "I'm trying to review the evolution of the development of a few programs. I've been away from this place for a while and I want to take the pulse of the biomedical community." . . . **PROMOTIONS IN** NCI's Div. of Cancer Prevention & Control: **Thomas Glynn** named Acting Associate Director, Cancer Control Science Program, succeeding **Claudia Baquet**; **Winfred Malone** is Acting Associate Director, Cancer Prevention Research Program; **Larry Friedman** is Acting Chief, Biometry Branch; **Marc Manley** is Acting Chief, Public Health Applications Research Branch; **Sherry Mills** is Acting Chief, Prevention and Control Extramural Research Branch.

NCI Holds Firm On ASSIST Budget, But Considers Adding Money Later

(Continued from page 1)

the $23.3 million proposed when the study was conceived (**The Cancer Letter**, Nov. 6).

The decision resulted in about 150 letters of protest to NCI officials over the past two months by the state health departments and volunteer organizations carrying out the study in 17 states. The ASSIST Scientific Advisory Committee and the ASSIST Coordinating Committee also protested the budget, as did the American Cancer Society. ACS is providing volunteers and cash worth about $20-30 million to the study.

The letters questioned whether the 20 percent reduction in the budget that NCI had planned to provide the states would compromise the ability of the study to reduce smoking rates.

Some of the letters said NCI's action was unfair and the Institute was reneging on a commitment it made two years ago when the contracts were awarded, sources told **The Cancer Letter.**

The letters were addressed to HHS Secretary Louis Sullivan, NCI Director Samuel Broder, Div. of Cancer Prevention & Control Director Peter Greenwald, and National Cancer Advisory Board Chairman Paul Calabresi. NCI staff is in the process of responding to the letters, sources said.

'We Did Not Promise A Specific Level'

Greenwald defended the decision on the ASSIST budget at a meeting of the National Cancer Advisory Board last month.

NCI's budget for cancer control is $105 million in FY93, $2 million less than last year. Funds for ASSIST rose $11 million from FY92 to FY93, Greenwald said.

"In a time of overall reduction of the [cancer control] line, the biggest increase of anything that we have done in prevention and control was to the ASSIST program," Greenwald said to the NCAB.

The division expects to spend $20.7 million of the cancer control budget on smoking prevention, and ASSIST will get $18.2 million of that, he said.

It is "not true" that ASSIST has taken a disproportionate cut among the programs in his division, Greenwald said. All of the prevention and control programs are funded at lower levels than what was requested in NCI's professional needs budget (bypass budget), he said.

"We feel that we do have a balanced budget and are giving a high priority to smoking prevention," Greenwald said.

"Was there a commitment made to a higher level, and was this then reduced?" NCAB Chairman Paul Calabresi asked.

"I would say no," Greenwald said. "There was an aim to fund at a higher level, but I talked with the ASSIST people myself, I met with them at meetings, and I told them very clearly, and it was in their contracts, that the level of funding depends on the availability of funds.... We did not promise a specific level."

Greenwald implied that one reason for the lower amount for ASSIST was that the final evaluation for its predecessor, the COMMIT trial, is not finished.

The COMMIT evaluation was supposed to be done this spring, and the analysis was to be used in estimating ASSIST funding, Greenwald said.

However, DCPC does not have the funds to complete the evaluation this year. The results will not be ready until January 1994, he said.

NCI could extend ASSIST one year to make up for the lower budget, Greenwald said.

'A 22 Percent Reduction'

NCAB member Erwin Bettinghaus, chairman of the ASSIST Scientific Advisory Committee, countered some of Greenwald's remarks.

"The original proposal and the basis on which all of the planning has taken place for the trial was, in fact, for a $22 million [FY93] budget for ASSIST, of which about $18.5 million was to be spent on the actual intervention itself," Bettinghaus said to the NCAB. The remainder of the funds were for the coordinating center and for evaluation.

Since the coordinating center's budget could not be reduced, the amount for the intervention will be $14.8 million, rather than $18.5 million.

"That is a 22 percent reduction," Bettinghaus said. "It is a little disingenuous to suggest that ASSIST

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went up significantly, because it almost had to go up" in order to carry out the intervention phase of the study, he said. The five-year intervention phase began this year, following two years of planning.

"One would expect a dramatic increase in the third year when you actually start doing something out in those states," he said.

New York's cut will amount to $388,000, Bettinghaus said. "They are now faced with the question of who and what do they cut. Do they cut direct intervention services? Do they cut their media budget? Do they not hire the specialized individuals who are going to be working in minority communities, for example? That is a difficult set of decisions for each one of the states to make."

The total amount for the trial--$135 million--also was announced by HHS Secretary Louis Sullivan, Bettinghaus said. That "solidified the states' belief" that NCI was "downscaling significantly from their original planning target."

Bettinghaus said he supported Greenwald's suggestion to extend the trial, and asked that NCI allow states to carry over funds that might be saved by reducing their planning efforts.

"The idea of carry-overs or extending the last year is something to consider, but we have to look at each grantee individually and see what they have accomplished and how it will be used," Greenwald replied.

'They Don't Buy This'

NCAB member Walter Lawrence, past president of ACS, said the Society felt NCI had "a certain commitment" to the study. "No amount of sleight of hand and manipulation of numbers like you have just done is going to convince them otherwise," he said to Greenwald.

"The people out in the 17 units all feel let down," Lawrence continued. "They don't buy this explanation that you just gave us, factual as it is."

NCI, he said, is trying to take its research and apply it to communities, "and we are all of a sudden failing. At least in the public relations standpoint we are failing."

Fought To Increase Prevention Budget

"This is a very complicated area, and we will certainly be receptive and look at all of the options that have been suggested," NCI Director Samuel Broder said to the NCAB.

Broder reminded the board that President Bush's FY93 budget proposed a $15 million cut in cancer prevention and control.

"We have had to struggle to fight to bring it back up to some moderate level where the patient still has a pulse, as opposed to an absolutely undetectable heartbeat," Broder said.

"We understand the importance of smoking, and we understand the importance of both ignited tobacco and cold tobacco as a carcinogen. So we understand all of those issues, and they are an inordinately high priority for the Institute.

"But, please, I ask all of you to understand the spirit of the things that we are trying to do or trying to accommodate. And that is, that while smoking is of surpassing importance and no credible cancer program can exist without having a very strong smoking cessation effort, there clearly are some crucial cancers for which smoking plays no apparent role."

For example, Broder said, he would "love to have" data linking smoking with breast or prostate cancer--two cancers for which Congress has told the Institute to increase research.

'We Can't Do Everything'

"There are many cancers that we have to deal with," Broder said. "I implore you all to please try, as difficult as it is, to think about the National Cancer Program as an entire entity. We can do any one thing that anybody wants. That is true. But we can't do everything....

"My prediction will be that this is not the last year that we are going to have a difficult fiscal reality."

Broder noted that NCI could cut 16 to 25 R01 or P01 grants to pay for ASSIST, or cut two new leadership initiatives for Hispanics and Appalachia, or cut the budget for the Cancer Information Service.

"If we have made a mistake or need to review the ASSIST program, we will do so," Broder said. "But if the attempt is to simply assert a political momentum ... that will mean that we can't have long range plans or we can't implement things across a diversity, but that what we will have to do is listen to who has the most fax machines and who has the most ability to get a political intervention....

"Among the things that we can do is to plan to bring in monies and build in an expectation that there will be funding through 1988," Broder said. "I would find it completely unsatisfactory to have to delay or undo a major study in breast cancer prevention, or any of several of the studies, if the sole goal is to meet the Year 2000 goals."

The goal of ASSIST is to speed the decline in smoking in the U.S. from the expected 22 percent in the year 2000 to 15 percent. That percentage was the target in NCI's "Year 2000" goals published in 1986.

Hope For Better Budgets

A question remains whether the ASSIST downscaling this year will affect the ability of the trial to achieve the desired reduction in smoking.

The Scientific Advisory Committee "couldn't come to the conclusion that it would not," Bettinghaus said to **The Cancer Letter** this week. The committee's letter to Broder raised the concern as a "general question," he said.

However, Bettinghaus said he admired Greenwald for standing by his decision after the deluge of letters.

"Rather than cutting everything by 3 or 5 percent, he made a harder decision," Bettinghaus said. "He was saying, 'We're willing to establish a priority, and you may not like this priority.' The quarrel, if there is a quarrel, is with NIH itself which removed dollars from NCI, and left Peter facing these decisions."

Helene Brown, co-chairman of the ASSIST Coordinating Committee, said that if the reduction stands, it should be a one-time cut that does not determine the level of funding in future years.

"I think the reduction is going to seriously affect the trial," Brown said to **The Cancer Letter** this week. "I hope they don't look at ASSIST as a savings account they can dip into anytime they need extra dollars.

"I have two hopes: One, that Congress will recognize the value of the program when giving NCI future budgets, and I will certainly try to alert them. And two, that future years budgeting will not reflect this cut."

Greenwald was invited to speak at the next scheduled meeting of the coordinating committee, May 13-14 in Washington, to answer questions of the ASSIST coordinators.

With No Input From Advisors, Healy Approves Compassionate Protocol

In the past three months, NIH Director Bernadine Healy has taken three different stances on the same issue: approval of a single-patient compassionate protocol for gene therapy in the case of a grade 4 glioblastoma patient.

▶On Oct. 22, Healy wrote that NIH could not approve a compassionate one-time use of gene therapy.

▶On Dec. 21, Healy wrote that NIH would be prepared to evaluate the patient for gene therapy at the NIH Clinical Center, but did not approve the patient's treatment of choice: a therapy designed by Ivor Royston, president and scientific director of the San Diego Regional Cancer Center.

▶A week later, on Dec. 28, Healy approved Royston's single patient gene therapy protocol. According to NIH, the decision was not to be regarded as "precedent-setting."

Healy was expected to explain her most recent decision at a special meeting of the Recombinant DNA Advisory Committee Jan. 14. She was also expected to ask the panel for guidance on compassionate use policy governing gene therapy.

Final Stance Most Controversial

Healy's final stance may be the most controversial of the three. In fact, one RAC member was said to have drafted a document arguing that Healy's decision violated the Institutes' own guidelines.

From the beginning, the problem seemed to defy a simple solution. The patient's husband, a prominent attorney and former federal official now residing in California, had done exhaustive research on gene therapy. In an interview with **The Cancer Letter** he said that earlier this year he had inquired about enrolling his wife in the NIH gene therapy program, but was told her chances of admission were slim.

Ultimately, he chose another form of gene therapy, one invented by Royston. The therapy involves growing the patient's own tumor cells in culture and transducing these cells with the IL-2 gene. These cells are then expected to act as a "vaccine" to stimulate an anti-tumor immune response.

Before he could administer the therapy, Royston had to obtain permission from both FDA and NIH. FDA clearance was relatively straightforward. The compassionate IND application was reviewed by the agency's staff and finally approved.

The approval by NIH was another matter. NIH has no mechanism for issuance of compassionate INDs involving gene therapy. It appeared that only RAC, a body that met four times a year, had the power to act on such urgent matters.

"You can't have a compassionate mechanism that meets four times a year," Royston said to **The Cancer Letter.**

As it happened, in the Sept. 25 issue of **The Cancer Letter**, Royston came across a story about a piece of legislation tacked on to the NIH appropriations bill by Sen. Tom Harkin (D-IA). Under the amendment, the NIH director was to be given the authority to permit any licensed physician to administer, for research purposes, "any medicine or medical procedure" when "there is no reason to believe that such medicine or medical procedure is unsafe."

The amendment, advocated by unconventional medical practitioners, appeared to fly in the face of the 1962 amendments to the Food, Drug and Cosmetics Act. Perhaps inadvertently, the amendment

seemed to give the NIH Director the powers that could be used to approve compassionate gene therapy protocols.

His own reservations about the amendment notwithstanding, Royston suggested that the patient's husband get in touch with Harkin.

As it happened, the patient was born in Iowa and her sister had worked on one of Harkin's campaigns. Though Harkin ultimately dropped the amendment, on Oct. 8, the Senator wrote a letter asking Healy or RAC to "give timely consideration to individual compassionate plea requests for approval of gene therapy procedures for terminally ill individuals.

"Such a step would be a temporary solution to this problem until an appropriate permanent legislative solution setting forth a clear authority and mechanism for handling these cases can be achieved next year," he wrote.

Harkin Ceases Involvement

The letter did not name the patient and, according to a staff member, Harkin has not been involved in the case since.

Responding to Harkin on Oct. 22, Healy wrote:

"Every patient treated with gene therapy thus far could qualify as a candidate for a compassionate plea exception. It is not possible to make decisions as to which case is more worthy than others when one is dealing with what are uniformly fatal diseases; attempting such kind of decisions would compromise the review process and not be in the best interests of such patients."

Meanwhile, the patient had undergone another experimental treatment, with radioactive monoclonal antibodies administered at Duke Univ. Despite the treatment, her tumor had increased by a third, Royston said.

With the patient's husband, Royston continued to press for NIH approval of a single-patient compassionate IND. In a Dec. 21 letter to Royston, Healy wrote:

"Recognizing the very urgent need in this case... we are prepared to see your patient immediately concerning possible entry into the protocol now active at the NIH Clinical Center (protocol 92-N-0246: Gene therapy for treatment of brain tumors using intra-tumoral transduction with thymidine kinase gene and intravenous ganciclovir.)...

"Considering that your own protocol has not yet achieved the necessary final approval... it would seem in the patient's best interest to have her evaluated at NIH, where a gene therapy protocol is already underway."

Also, Healy scheduled a special meeting by RAC to consider Royston's request for Jan. 14.

However, on Dec. 28, a letter from NIH Deputy Director Lance Liotta informed Royston that "pending final FDA approval for safety, Dr. Healy has approved your compassionate plea request for a single patient gene therapy. In view of the crucial nature of the RAC review, this one-time decision is non-precedent setting and will not create any rights, interests or obligations for you or any other investigators in the future."

The patient has since received gene therapy, Royston said.

Next week: RAC discusses the case, Healy's action, and future policy.

NCI To Fund 3,232 Research Grants In FY 93; 873 Competing Grants

NCI expects to fund 3,232 research project grants in FY 1993, according to budget documents released this week. Following is the breakdown by mechanism showing how the Institute expects to spend its FY93 appropriation (figures include spending on AIDS):

Research project grants:
--2,359 noncompeting grants at $687.7 million;
--873 competing grants at $224 million;
--administrative support costs of $6.5 million;
Total 3,232 RPGs for $918.45 million.

Research centers: 74 funded at $145.8 million.

Other research: includes clinical education and career awards, 784 grants for $111.69 million.

Training:
--Individual: 150 awards for $4 million.
--Institutional: 1,311 awards for $33 million.

Research & Development contracts: 355 contracts for $195.2 million.

Intramural research: $364 million.

Research management and support: $96 million. This line includes the Office of Cancer Communication, and several other information and outreach programs.

Cancer control: $105 million.

Construction: $7.6 million.
Total NCI final appropriation: $1.981 billion.

DCPC Advisors OK Minority CCOPs, RFA In Native American Women

Advisors to NCI's Div. of Cancer Prevention & Control gave concept approval to continuation of the Minority-Based Community Clinical Oncology Program, which works to increase accrual of minorities to cancer clinical trials.

DCPC's Board of Scientific Counselors also gave concept approval last week to a new RFA for prevention and control studies in Native American women, and approved recompetition of an RFP for chemoprevention studies.

NCI funded 12 Minority-Based CCOPs in 1990. Last year, the first year of non-developmental funding, the CCOPs accrued 470 patients to treatment trials and 423 patients to cancer control trials, according to the concept statement.

The 10 currently funded MB-CCOPs contributed more than 10 percent of all minority accrual to NCI sponsored treatment trials. According to a recent survey, 14.1 percent of all patients entered onto NCI sponsored treatment trials were ethnic minorities.

An evaluation of the program said the MB-CCOPs face significant barriers and limited resources, but are developing innovative approaches to improve accrual.

Following are the concept statements:

Minority-Based CCOPs. Continuation of an RFA (cooperative agreements), $2.7 million in FY94, $3 million in FY95, $3.2 million in FY96, and $3.3 million in FY97; 12 awards. Program director: Otis Brawley, Early Detection & Community Oncology Program.

The goal of this concept is to continue the Minority Based-Community Clinical Oncology Programs (MB-CCOPs). The objectives of the MB-CCOPs are to:

--Bring the advantages of state-of-the-art treatment and cancer control research to minority individuals in their own communities by having practicing physicians and their patients/subjects participate in clinical treatment and cancer control research protocols;

--Provide a basis for involving a wider segment of the community in clinical research by increasing the involvement of primary health providers and other specialists (e.g., surgeons, urologists, gynecologists) with the MB-CCOP investigators in treatment and cancer control research, thus providing an opportunity for education and exchange of information;

--Provide an operational base for extending cancer control, and reducing cancer incidence, morbidity, and mortality in minority populations by accelerating the transfer of newly developed cancer prevention, detection, treatment, and continuing care technology to widespread community application;

--Facilitate wider community participation in future treatment and cancer control research approved by NCI; and

--Examine selected issues in MB-CCOP performance (e.g., patient recruitment, accrual, eligibility) and evaluate its impact in the community.

Respondents to this initiative must have access to a large minority cancer population (e.g., greater than 50 percent of new cancer patients) and a demonstrated potential to participate in NCI-approved clinical trials and cancer control activities. The applicant may be a clinic, a group of physicians, a hospital, a health maintenance organization, a consortium of physicians and/or hospitals and/or health maintenance organizations that agree to work together with a principal investigator. Primary teaching hospitals medical schools with large minority populations may apply. A Veterans Administration hospital may participate as a non-dominant member of a consortium led by a minority-based institution.

The applicant must have adequate facilities, a potential to conduct clinical research, and an interest in participating in cancer control research. University hospitals participating as Cooperative Group members funded through the Div. of Cancer Treatment will not be eligible. Unfunded, non-university group members will be eligible.

Applicants must provide a plan for data management support, patient follow-up capability, and quality control procedures. A description of the organizational plan, relationship of the organizational leadership to the fiscal agency and other consortial components, line of responsibility from key support personnel to the organizational leadership, and procedures for monitoring and evaluating the progress of the program in meeting its accrual goals should be described.

Participating physicians will be required to enter patients onto NCI-approved protocols through one or more NCI-funded research bases (cooperative groups or cancer centers). The research bases will be responsible for protocol development in treatment and cancer control research and for data analysis and monitoring. Research base sponsored treatment and cancer control protocols must be approved by the appropriate DCT or DCPC protocol review committee. MB-CCOP and research base activities must also conform with Office for Protection from Research Risk regulations on research in human subjects.

Required Activities:

Patient accrual to clinical trials is expected to be reflective of the new cancer patient distribution of the participating physicians; that is, greater than 50 percent of new cancer patients from minority populations. Each MB-CCOP is expected to accrue a minimum of 50 credits per year in research base sponsored cancer treatment clinical trials that are approved by the Protocol Review Committee, DCT, NCI. For applicants whose specialty is pediatrics, the 50 credit minimum requirement may be waived for those who are able to place a majority of their eligible patients on protocols. In the first year of funding, each MB-CCOP will be expected to accrue a minimum of 20 credits per year to cancer prevention and control protocols that have be approved by the Cancer Control Protocol Review Committee, DCPC and/or the the Protocol Review Committee, DCT. In succeeding years the cancer control credit requirement will be raised.

Each MB-CCOP may affiliate with up to five eligible research bases, one of which may be a national multi-specialty cooperative group. If participation in the protocols of one group competes with that of another group with which the MB-CCOP is affiliated (e.g., two adjuvant protocols for the same eligible Stage II node positive patient), the MB-CCOP

must prioritize the protocols in order to avoid bias in the allocation of patients to competing protocols.

MB-CCOPs are closely monitored through a combination of program site visits, annual progress reports, the patient log, and audit reports from affiliated research bases. The inability of a MB-CCOP to meet the performance requirements set forth in the Terms of Cooperation in the Request for Applications, or significant changes in the level of performance, may result in an adjustment of funding, withholding of support, suspension or termination of the award.

Native American Women's Cancer Initiative. Proposed new RFA, $1 million per year, four years, up to five awards. Program director: Linda Burhansstipanov, Special Populations Studies Branch.

The goal of this concept is to improve cancer survival rates and reduce cancer mortality rates in Native American women through prevention and control efforts.

Objectives are:

--To address the barriers to access culturally appropriate quality cancer control services including screening, appropriate followup, diagnostic, treatment and rehabilitation programs for cancers which are common and/or disproportional within indigenous women.

--To reduce cancer risk behaviors in Native American women (e.g., high dietary fat intake, tobacco use, alcohol consumption).

--To increase the number of Native American women who are in key research positions (eg, principal investigators) by improving their research skills.

The NAWCI will address cancer prevention and control with Native American women through an RFA which has three options. The investigator must specify the option in the application.

Option A: Common/Disproportionate Cancer and Barriers.

Cancer Intervention Research in Native American Women grants which focus on cancers which are more common among Native American women and supports the development of long-term intervention strategies. These projects will address the barriers which Native American women experience to access culturally appropriate quality cancer control services including screening, appropriate follow-up, diagnostic, treatment and rehabilitation programs. The efficacy and effectiveness of culturally appropriate interventions which reduce the barriers to screening, early detection, and state-of-the-art treatment will be assessed.

These projects will focus on cancers which are more common among Native American women from a specified area (e.g., breast cancer among Native Hawaiian women, or gallbladder cancer among Southwestern Indian women, or lung cancer among Alaska Native women), or they may address the unusually aggressive forms of cancers in Native American women (e.g., young Southwestern American Indian women progressing from Class 11 Pap smear to invasive cervical cancer within 24 months).

Option B: Risk Factors.

Cancer Risk Factors among Native American Populations RFA will assess the cancer prevention and control risk factors of this population in regions of the country where the cancer control needs of American Indian and Alaska Native have been increasing and data are sparse (eg, Northern Plains region, Northwestern US, Northeast US, Southeast US, remote Alaska Native villages). Unusual behaviors, such as frequent use of smokeless tobacco, or high consumption of smoked, high fat foods; or access to high fat commodity as a sole source of food availability may be emphasized.

Option C: Research Capacity Development.

Research Capacity Development Workshops will be designed to provide technical assistance to increase the research application and scientific skills of American Indian and Alaska Native women. The aim of these workshops is to increase the number of Native American women who pursue research careers and/or become co-investigators or principal investigators of NCI research projects. These grants would involve offering workshops in different hard-to-reach Native populations and providing them with technical assistance in the development of research ideas and applications. The Research Capacity Development workshops will be limited to human research and the clinical-behavioral fields only.

Efficacy Studies of Chemopreventive Agents in Animal Models. Continuation of a Requests for Proposals-Master agreements, $1.2 million per year, four years, estimated four to six master agreement orders issued annually. Project officers: Vernon Steele and Gary Kelloff, Chemoprevention Branch.

The primary objective of this study is the evaluation of efficacy of various selected chemopreventive agents at several dose levels in animal models. The animal models are organ specific and are chosen for their relevance to the human cancer problem. As such they include respiratory tract, colon, breast, and bladder. The agents chosen for efficacy studies are ones with strong indications of cancer preventing activity from the published literature, and the Chemoprevention Branch's own in vivo and in vitro screening efforts. Depending upon the agent and available data, efficacy testing may include a detailed examination of dose response, bioavailability, organ site response, and potential toxicity. Combinations of promising chemopreventive agents and inhibition of initiation as well as promotion will be examined by this contract.

Master Agreements will be issued to all investigators or institutions who are deemed via peer review to be qualified for carrying out whole animal efficacy tasks. The MA to investigators or institutions will be for a period of four years. All offerors for MA will be asked to submit a sample protocol (for an animal efficacy study in at least one target organ including lung, colon, mammary gland, bladder or a model they feel is relevant to the human cancer problem) in their technical proposals. This proposal should detail all aspects necessary for the study including staffing, scheduling, organization, equipment and facilities.

As agents are nominated and selected for efficacy testing, applications for Master Agreement Orders will be requested from MA holders via a Request for Proposal. The proposals in response to the RFP will be peer-reviewed and the best proposal selected for funding and implementation. Up to ten new agents or combinations of agents will be studied each year. The number of studies and target organs will be determined as necessary for each compound evaluated. Such efficacy studies may include: 1. Dose response studies. 2. Combination studies. 3. Bioavailability studies. 4. Detailed pathological studies. 5. Chemical/biological class studies. 6. Pharmacokinetic studies. 7. Continuous vs intermittent dosing

studies. 8. Evaluation of new organ specific animal models. 9. Bioassay of chemopreventive agent induced physiological effects.

A standardized protocol will be developed by the Chemoprevention program for each target organ model and for controls, statistically valid group sizes, number of doses of chemopreventive agents, number of doses of carcinogen, standardized test for purity of the agent and preparation of the agent in the diet, standardized test for assay of the agent (in food and in sera), criteria for animal evaluation including source, care, monitoring, and pathology evaluation.

RFAs Available

RFA CA-93-10
Small grants for clinical trials in AIDS malignancies
Letter of Intent Receipt Date: Feb. 1
Application Receipt Date: April 23

The Cancer Therapy Evaluation Program of NCI's Div. of Cancer Treatment invites small grant applications for innovative therapeutic studies in AIDS malignancies. Studies should be restricted to pilot or phase I or II trials with 5 to 30 patients/trial.

Domestic for-profit and non-profit organizations, governments and their agencies are eligible to apply. Applications can be from single institutions or multiple institutions (collaborating institutions, consortia, cooperative groups). New and experienced investigators, and women and minorities are encouraged to apply.

Support will be through the NIH small grants mechanism (R03), which provides limited funds (maximum of $48,000 direct costs per year) for short-term (up to two years) research projects. The R03 grants are not renewable. Future competing renewals (type 2s) must be submitted as traditional research grant applications (R01s).

Approximately $750,000 in total costs per year for two years will be committed. Ten awards will be made in FY 93. The total project period may not exceed two years.

Research Goals: The aim of this RFA is to stimulate pilot, phase I, or phase II therapeutic clinical trials in AIDS malignancies so that new treatment strategies and new agents are moved more rapidly into the clinic. The ultimate goal of the NCI is to provide more effective management and treatment for HIV-associated malignancies in children, and adult men and women.

Examples of potential clinical studies: 1) combinations of interferon-alpha and/or retinoic acid in anogenital dysplasia or cancer; 2) angiogenesis inhibitors in Kaposi's sarcoma; 3) immune modulating therapy with IL-4 (and subsequent down-regulation of IL-6, which may have some role in the development of NHL or Kaposi's sarcoma), anti-B4 blocked ricin immunoconjugate in NHL, or anti-sense to potential viral cofactors such as HPV in Kaposi's sarcoma.

Although the major purpose of these grants is to facilitate rapid testing of novel agents or innovative approaches, tumor tissue or other relevant biologic fluid collection is strongly encouraged for ongoing or future investigations of laboratory correlates. The interchange of ideas and tumor tissue between the recipients of the grants will be encouraged.

Inquiries may be directed to Dr. Roy S. Wu, Cancer Therapy Evaluation Program, Div. of Cancer Treatment, NCI, Executive Plaza North Room 734, Bethesda, MD 20892; phone 301/496-8866; fax 301/480-4663.

RFA CA-93-16
SPORE in gastrointestinal cancer
Letter of Intent Receipt Date: Feb. 26
Application Receipt Date: April 23

The Organ Systems Coordinating Branch of NCI's Div. of Cancer Biology, Diagnosis and Centers invites grant applications (P50) to establish Specialized Programs of Research Excellence that focus on human gastrointestinal cancers of highest incidence and mortality. These programs will be established at institutions that will make strong commitments to the organization and conduct of these programs. Each SPORE must be dedicated to translational research which moves basic research findings into more applied research settings with patients and populations in order to have the most immediate impact possible on improving cancer prevention, diagnosis and treatment and on reducing cancer incidence, mortality and morbidity. This could include areas such as the development of new diagnostic and prognostic tests, the conduct of innovative therapeutic protocols, the development of new primary and secondary prevention measures, as well as cancer control studies and studies that encompass rehabilitation and quality-of-life research.

Each SPORE must 1) both address colorectal cancer and mount a significant effort on pancreatic cancer; 2) represent a collaborative enterprise between basic and clinical scientists in the conceptualization and implementation of research projects; 3) develop and maintain human cancer tissue resources that will benefit translational research in these cancers; 4) develop extended collaborations in critical areas of research need with laboratory and clinical scientists in the parent institution and in other institutions; and 5) participate with other SPOREs and/or NCI on a regular basis to share information, assess scientific progress in the field and identify new research opportunities for reducing colorectal and pancreatic cancer incidence and mortality, and for increasing and improving survival. Each SPORE must support a mix of basic and clinical research and focus on human disease.

To be eligible, applicant organizations must have 1) a minimum of three independent investigators who are successful in obtaining peer-reviewed research support directly related to gastrointestinal cancer, and who represent experience in both laboratory and clinical research. An alternative is a minimum of three independent investigators each having published articles that significantly address gastrointestinal cancers in peer-reviewed research journals and who combined represent experience in both laboratory and clinical research; 2) access to a patient care and service facility that serves gastrointestinal cancer patients and, if the facility is not part of the parent institution, a statement signed by the responsible officials of the applicant institution and the consortial care facility that assures access to gastrointestinal cancer patients for clinical research.

NCI anticipates making one or two awards for initial project periods of three years and anticipates a $1.5 million will be set aside for the initial year's funding. Applicants may apply for part or all of the $1.5 million. High quality applications not fundable in FY93 may be considered for FY94.

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