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P.O. Box 2370 Reston, Virginia 22090 Telephone 703-620-4646

NCI EASES SOME COOPERATIVE GROUP CONCERNS; DEVITA CONSIDERS OTHER CCOP-RESEARCH BASE FUNDING OPTIONS

The cooperative groups, beset by what many of their members perceived as unrealistic and unstable NCI requirements, severe budget limitations and impingements threatened by the advent of new regional groups and the Community Clinical Oncology Program, have received some assurances recently from NCI. These include:

• The demand for multimodal studies generated in the mid-1970s which some groups have not been able to undertake successfully have been eased. *(Continued to page 2)*

In Brief

NEW DRCCA RECRUITS: CULLEN WILL BE GREENWALD'S DEPUTY, FRELICK TO BECOME CCOP PROJECT OFFICER

JOSEPH CULLEN, deputy director of the UCLA Jonsson Comprehensive Cancer Center and director of the Cancer Control Program there, will rejoin NCI in June as deputy director of the Div. of Resources, Centers & Community Activities. **ROBERT FRELICK**, head of the section of oncology at the Wilmington, Del. Medical Center and former president of the Assn. of Community Cancer Centers, also will go to DRCCA in June as project officer for the Community Clinical Oncology Program. Cullen, a physiological psychologist with a PhD in that specialty from Florida State Univ., was at NIH in 1973 as a grants associate when the NCI Cancer Control Program was initiated. He became head of review activities in treatment and rehabilitation for the program, then later was program director for behavioral projects. He left in 1976 for UCLA and since has become a spokesman of national stature for cancer control and psychosocial aspects of cancer. Frelick received his MD from Yale and did his residency at Memorial Hospital in New York. He has been in private practice since 1950, and was "an early medical oncologist, before anyone had a name for it." Cullen and Frelick will join Jerome Yates, who will head the Centers & Clinical Oncology Program, on the DRCCA staff as DRCCA Director Peter Greenwald aggressively recruits outside talent. . . . **ORGAN SITE** Program funding, following the decision to hold the payline to the 180 priority score, is as follows: 94 noncompeting renewals, $9.85 million, plus administrative supplements totaling an estimated $500,000; 35 competing renewals under the 180 payline, totaling $2,885,000. That will leave $535,000 in the total budget of $13,770,000. There were 47 approved new grants, with 19 of them under the 180 payline. Those 19 had budgets of $1.6 million, so obviously all of them cannot be paid from the existing budget. If new and competing renewals are paid to the same priority score, the payline would be approximately 174. The decision by NCI at the moment is to not pay any new organ site grants, but that could change.

FORMAL DISEASE COMMITTEE RATING GOAL OF NEW GUIDELINES FOR GROUP REVIEW

(Continued from page 2)

• The Cooperative Group Cancer Control Program, which makes available about $5 million a year to assist participating groups in bringing community physicians and their patients into clinical trials, will be continued for a minimum of two years, probably three, and possibly indefinitely.

• The CCOP RFA will provide maximum flexibility in administration of the relationship between the community organizations and the cooperative groups and university centers.

• The new guidelines being developed for the Cancer Clinical Investigation Review Committee for reviewing the groups, which will formalize the prioritizing of disease committees, are still being written and probably will not result in any immediate major changes in funding of groups.

Bruce Chabner, acting director of NCI's Div. of Cancer Treatment, was present at the last meeting of the CCIRC, committee Chairman Joseph Simone said, "because some important issues have been raised. Just what is the policy on the multimodal approach to clinical trials? How much is it a requirement? How much does it influence the evaluation of a grant? What is the relative value of science versus patient accrual? That's a question we are constantly strugging with."

"What we want out of the clinical trials program is good quality science," Chabner responded. "We don't want to proscribe specific multimodality requirements. We want high priority, high quality clinical trials with modalities as required to do them. It shouldn't be the requirement of every group to have equal representation of all four specialties, including immunotherapy. It is not a uniform and necessary requirement. First, consider what the group is trying to do, the scientific objectives of the group. Second, on the relative issue of patient accrual versus scientific input, if a group member makes a great contribution to the science but brings in only a few patients, if that member is essential to the group, don't disable it by cutting him off. Accrual is important, but just placing large numbers of patients on protocols is not sufficient for continued funding. Judge individual members on the scientific design of high priority protocols and their ability to put patients on those protocols."

The new guidelines "will not change the requirement for good science," Chabner said.

"Will group chairmen prioritize their own protocols?" committee member Diane Komp asked.

"No, that's your job," Chabner answered. "It's up to the individual group to decide what it does best, and to you to pick out what is important."

"This is a new concept from NCI," Komp said. "It will be harder than you perceive to make these judgments."

"Good science stands on its own," committee member Roy Weiner said. "This will be a distinct change from the philosophy imposed on the groups to embrace the multimodal concept. It will require a period of time to adjust. Part of the urgency to tighten up is coming from the new mechanisms, CCOP. NCI has the opportunity to encourage those groups to adhere to the same stringent criteria now being imposed on the national groups. This attempt to seduce private practitioners to participate in clinical trials could take money away from established groups."

"I don't want to get into CCOPs," Chabner said. "That's controversial enough. It's not much different from the (cooperative group) outreach program. Some groups have done very well with their outreach efforts."

"It may be difficult for a group to get a grasp on what its scientific priorities are," committee member Omar Salazar said.

"Try to come up with scientific judgments of disease committees," Daniel Kisner, acting director of the Cancer Therapy Evaluation Program, said. "The implied mandate for multimodality should not be considered a mandate for mediocrity."

"A group is a team effort," committee member Joseph Eggleston said. "Not everyone plays the same position."

"The concept of medium, high and low priority is a good one, committee member Harold Maurer said, referring to the staff's recommendation that disease committees be rated in that manner. "But it opens a bag of worms. Medium and low priority committees are not likely to be funded. Even some high priority ones may not be. You can take a low priority study and come out with a high priority yield, and the reverse."

"You can't expect the grant mechanism to fund on a blank check basis," Chabner said. "The idea of assigning scientific priorities is essential, and it is surprising that we have gone this far without it."

"Concentrate on study design quality rather than mechanism," committee member Hugh Davis said. "Cooperative groups in many ways are large program projects. The review committee will have an awful time if it tries to look at every little exigency. If a study does not look good overall, just say it's out, rather than try to cover all modal bases. If an institution puts all of its GI patients on an abysmal study, tell them to go elsewhere for funding."

Dorothy Macfarlane, CCIRC executive secretary, said the new guidelines will be sent as a memo to group chairmen, and instructions for reviewers are being rewritten.

"Will you require a separate budget from each disease committee so if you drop one, it's clear cut?"

asked committee member Robert Lindberg.

"That's not completely decided," Kisner said. "My feeling is that there's a way to do it. DCT would like to have money going to individual institutions linked to scientific contribution."

"Throughout cooperative group review, there has been an unanswered question, the cost of doing business," Weiner said. "The concept of a core plus individual project costs is an attractive one, I think."

"Do as we do now," committee member Harvey Preisler said. "Give the money to the groups and let the groups be accountable. The overall group should have a priority score and each individual funded on the basis of his contribution."

"It's legitimate to have each group set its own priorities," Preisler said.

"They do that now," Weiner said. "They strut their best stuff for site visitors. We all do."

"It's up to the people writing the application to make clear what they do best, and their track record," Chabner said.

"What do we do about institutions that attract only certain kinds of patients, and may not be in a position at all times to put patients on high priority protocols?" committee member Janet Wolter asked.

"That can only be taken into account by assigning low priority scores," Chabner said. "We don't have enough money to fund someone just to keep them involved."

"I'm concerned about the perception that this is a sudden change," commented Edwin Jacobs, associate chief of the Clinical Investigations Branch. "That is not the case. Cooperative groups have been reviewed three times, at the Williamsburg conference in 1969, the Potomac conference in 1975 and by the DCT Board of Scientific Counselors in 1979. These principles were included in those reports."

Macfarlane said the review would rate disease committees "strong, average, or weak," with these questions in mind:

"1. What is patient accrual at this institution to high quality protocols?

"2. What is the scientific contribution to high quality areas?

"3. Is modality strength sufficient for high quality contributions?

"4. Are data timely and of high quality?"

"It has to be borne in mind that the cooperative groups have some unique characteristics," committee member Laurence Baker said. "One example is the ability to study rare diseases. I have no doubt that a single institution can perform high quality science but the ability to study rare diseases must be kept in mind. One criterion in the review should be how well does this group use its unique resources."

"The new guidelines in effect will dismantle the multimodal concept," Eggleston said. "We'll see this over and over: leukemia and lymphoma in a group will be rated high, small cell carcinoma good, and GI and melanoma, low. The group will tell the surgeons to remain in the background during the review, while pushing the leukemia and lymphoma committees. The Potomac conference dragged us in kicking and screaming. If you want us to leave, we will."

"Our hope is for an institution that does well in one area to be recognized," Macfarlane said.

"If the problem is funding, we should concentrate on doing what we are doing a little better," Maurer said. "More stringent in science but don't limit flexibility."

"How would you evaluate an institution?" Macfarlane asked.

"By the priority score," Maurer replied.

"How do you give a priority score to an institution?" Simone asked. "It gets down to things like, do you go to meetings, etc."

"Stress what unique contribution the institution makes to group studies, and patient accrual," Weiner said.

The discussion ended with a comment by Davis, "The eulogies for the multimodal concept are entirely premature."

The Cooperative Group Cancer Control Program has been crucial for some groups, providing 30 percent or more of their patients.

The program's original five year contracts end this year, but the Div. of Resources, Centers & Community Activities Board of Scientific Counselors in January approved recompetition for two more years. Some members felt that the program should not have been extended at all, counting on CCOP to take over the role of providing the flow of patients from communities to the groups.

The majority decided that the CCOPs might not be up and operating that soon, a wise decision since the CCOP RFA has yet to be written and the first CCOP dollar will not be awarded before March 1983.

NCI Director Vincent DeVita and DRCCA Director Peter Greenwald had hoped the CCOP RFA would be out by now, but the decision by the National Cancer Advisory Board's Subcommittee on Clinical Oncology & Communities to delay the RFA until after the full NCAB meeting in May ruined that schedule.

Greenwald told the Cooperative Group Chairmen's Executive Committee last week that because of the delay, the group cancer control contracts would be recompeted for three years instead of two. A hitch developed immediately, when DRCCA staff found out that the extra year could be added only by withdrawing the two year RFP and issuing another. That would delay the new awards until long after the existing contracts with their seven month administrative extensions had expired.

So the two year recompetition remains in effect,

but the prospect is good that NCI will seek authorization for a noncompetitive extension for a third year at the appropriate time. By then, the impact of CCOP may be more apparent, and it is possible that DRCCA will ask its Board for concept approval of another three or even a five year recompetition if it seems that the two programs complement each other well enough to coexist indefinitely.

In any case, DeVita assured the chairmen's executive committee, "We never had any intention of doing anything with CCOP that will hurt the groups." He acknowledged that some problems could arise as community hospitals presently affiliated with the groups change over to CCOP. But community institutions, to participate in CCOP, will have to provide a flow of patients into group and/or center clinical trials, and DeVita said he is confident the new program will prove to be a major benefit to the groups.

DeVita has insisted all along that research bases would have to get their money for participation in CCOP through the community organizations. He told the chairmen's executive committee, however, that he is now willing to consider other options.

Group and center executives have said that dealing with a multitude of subcontracts would be an administrative nightmare. When Paul Carbone suggested another approach—require CCOPs to complete negotiations with research bases before they submit their applications but then permit the groups or centers to apply for one supplemental award to cover all their agreements—DeVita said "that's reasonable."

DeVita later discussed the issue with ***The Cancer Letter.*** "I think that we had better leave this one open, and not dictate what they will have to do. I think we ought to spell out what the options are. We need to bring in the business people at this point. We're down to the nuts and bolts, the mechanical issues."

Thus, when the RFA is written, it probably will offer several approaches from which the community organizations and research bases may choose, depending on what the grants administration staff comes up with.

Discussion at the Chairmen's Executive Committee meeting touched on:

—Overhead. "I don't know what community overhead will be," DeVita said. "I suspect it will not be insignificant. I prefer to let the RFA go out and them negotiate."

"Some institutions are not entitled to overhead," Marvin Zelen said. "Some may not know how to go about it."

"They learn quickly," Bernard Fisher added.

—Geographic limits. Executive Committee Chairman John Durant asked how geographic areas would be defined. "I can see some overlaps causing problems."

"That depends on how they come in," Greenwald said. "Service areas will have to be defined in the applications."

"Determining the nearest center geographically has worried some people," DeVita said. "It's obvious that if there are three centers in one city, it will not make any difference geographically which is the research base for a CCOP in that city. The same might apply to a center in a nearby center. We're not going to worry about a few miles. But if the variation is from 100 miles to one center and 300-400 miles to another, we will." NCI has insisted that CCOPs not "skip over" centers for research bases but negotiate with those in their respective regions.

—The tithe. "The sticking point is when you get to 10 percent of what?" Durant said.

"The tithe is nothing more than a governor," DeVita said. "That is meant to be the basis for negotiation. What it means is that you won't have to take 50 patients with carcinoma of the epidermoid if you don't want them. At the workshop in Los Angeles, one physician said his institution could put 50 breast cancer patients on protocols. We said that would be allowable if it is permitted in the negotiations with the research base.

"The problem with demanding that only those community hospitals with track records be allowed in the program is that you would exclude most of those we are trying to get at," DeVita said.

"There have been only two institutions in the NASBP that have put as many as 50 onto protocols in one year, and one of them was the Univ. of Pittsburgh," Fisher said. "One concern we have is that in the negotiations with research bases, some other group will say, sure, we'll be glad to take your lymphomas, etc., but we have breast cancer protocols, too, and you'll have to participate in those. We're a bit edgy, we do perceive it as a problem."

"It could be, but I don't think it will," DeVita said. "I have never sensed this will impact severely on NASBP."

"I would like to see more cohesion rather than splintering up the cooperative groups," Fisher said. "In breast cancer studies, with the need to look at all the subsets of patients, we need thousands, not 500 or 600."

"There are untapped resources out there," DeVita said. "You'll get your thousands of patients, and in one year, not three."

"It's an exciting prospect," Fisher said. "I'm for CCOP. It's an extension of what we are doing now."

"One thing I can guarantee is that when the RFA hits the street, NCI staff will go out and help deal with problems arising in the negotiations," DeVita said.

"Are you saying that despite all these rules, you're going to be very flexible in the review of those applications?" Durant asked.

"We have no other choice," DeVita said. "We'll take them as they come."

CROUT, FINKEL REPLACED AT FDA, HAYES COMBINES DRUGS, BIOLOGICS BUREAUS

When the NCI-FDA relationship hit bottom in the mid-1970s over clinical trials with investigational anticancer drugs and FDA's regulation of them, Vincent DeVita, then director of the Div. of Cancer Treatment, and Richard Crout, head of FDA's Bureau of Drugs, took the issues in hand and worked out the problems themselves.

DeVita has credited the friendly working relationship developed with Crout and with Marion Finkel, chief of new drug evaluation at FDA, with smoothing out the problems, speeding up approval of INDs, development of the Group A, B, and C distribution system, agreements on monitoring and reporting, and approval of the new toxicology protocol.

That relationship has now ended. Crout, who said nearly two years ago that he wanted to leave FDA but would stay on until a replacement was found, has left. FDA Commissioner Arthur Hayes has combined the Bureau of Drugs with the Bureau of Biologics, and the director of the new bureau is Harry Meyer Jr., who has been head of biologics.

Finkel has been transferred to a new orphan drug development office. Her replacement, on an acting basis, is Robert Temple, head of the cardio-renal drugs division.

ACS PRESIDENT CALLS ON REAGAN TO BACK NEW LEGISLATION ON CIGARETTE WARNING

The American Cancer Society has appealed to President Reagan personally for his support of legislation which would strengthen the health warnings on cigarette packages and in cigarette advertising. The Administration, after first expressing enthusiastic support for the legislation, backed off when the tobacco lobby and tobacco state congressmen went to work.

Robert Hutter of Livingston, N.J., ACS national president, said this week that the Society has sent a letter to the President asking him to throw his full support behind the legislation, whose authors are Congressman Henry Waxman (D.-Calif.), Sen. Orrin Hatch (R.-Utah), and Robert Packwood (R.-Ore.)

"I've advised the President that we look to his leadership as a major source of strangth and resolve for us, the private, nonprofit voluntary health agencies, in our battle against such an insidious health hazard as cigarettes, which jeopardize the lives and well being of our citizens, especially our young people," Hutter said.

The proposed law, known as the Comprehensive Smoking Prevention Education Act of 1981, would require more specific statements describing the health hazards of smoking on cigarette packages and in advertisements. It also would make it mandatory for manufacturers to make known to government agencies the substances used as additives in cigarettes, which they are not now required to do. In addition, it would establish the Office of Smoking & Health as a permanent resource in the Dept. of Health and Human Services.

Hutter commented that scientists appear to be losing the war against cancer only because death rates from cancer of the lung keep going up. "We're winning the war on most cancers," he said, "but the specific battle with lung cancer is very difficult."

He pointed out that while the death rate for all forms of cancer combined increased by about eight percent in three decades ending in 1980, they actually show a decline of 10 percent when the figures for lung cancer are excluded.

Between 1950 and 1980, he said, lung cancer mortality increased 224 percent in the United States—175 percent for males and 250 percent for females.

Hutter called attention to recent innovations in cancer therapy which he said have provided new "incentives" for apparently healthy people who harbor incipient cancers to seek early diagnosis and treatment. Since these therapies are less debilitating, the patient has less to fear. Simpler forms of mastectomy are being used, and radiation therapy has become a primary treatment modality for some breast cancer patients. Operations in selected early cases make some colostomies unnecessary and therefore have made rectal cancer less worrisome, and new combinations of therapy have eliminated the need for amputation in some cases of bone and soft tissue cancer.

Hutter said that the Society's upcoming Cancer Prevention Study, which will keep track of more than 1 million American adults for at least six years, will cost the Society only about $12 million because it will be carried out by approximately 80,000 volunteers. "If it were done by paid interviewers," Hutter declared, "the cost would exceed $100 million and would, of course, be prohibitive."

"It is propitious," he commented, "that the ACS planned to start this study coincident with the introduction of the 'New Federalism' and the governmental challenge to the private sector to assume increased social responsibility."

The American Cancer Society has expended more than half a billion dollars on cancer research since 1946, he pointed out.

CANCER CONGRESS SCIENTIFIC PROGRAM TO UPDATE BASIC, CLINICAL SCIENCE

The scientific program planned for the 13th International Cancer Congress, Sept. 8-15 in Seattle, sponsored by the International Union Against Cancer (UICC), will provide a major opportunity for interactions and updating in the various fields of oncology, including preclinical and clinical sciences, and

allied disciplines, Secretary General Edwin Mirand said.

Major emphasis will be given to the following areas:

- The most significant advances in clinical investigations that have occurred since the 12th International Cancer Congress, 1978.
- Progress in understanding the mechanisms of cell growth control and cell differentiation.
- Identification of biological responses that define tumor-host relationships.
- Development of new therapeutic approaches based on these advances.
- Progress is clarifying the mechanisms of chemical carcinogenesis and the genetic and environmental factors conditioning the development of cancer; and those factors related to socioeconomic and geographic influences.
- Subjects related to patient care and its organization, with particular emphasis on the indispensible functions of the professional nurse and the need for complex supportive structures that are essential in both the hospital and community setting for optimal delivery of care to cancer patients.

Progress in managing most neoplastic diseases in humans will be extensively review. Examples include:

—Advances in management of lymphomas, including improved diagnosis, classification and staging, including use of such approaches as monoclonal antibodies. Emphasis will be given to the responses of this disease to combined modalities of treatment, particularly those involving radiotherapy, and the use of novel therapeutic approaches, including interferons.

—Progress in the management of malignant melanoma, particuarly the use of surgical procedures and results of chemoimmunotherapy. Problems in diagnosis, classification and prevention will also be considered.

—Improvements in the management of breast cancer. Topics: the diagnosis and treatment of minimal breast cancer and the role of radiation treatments; progress in adjuvant chemotherapy and the definition of optimal surgical treatments; signficance of therapy and the definition of optimal surgical treatments; significance of multidisciplinary approaches to the diagnosis of breast cancer, of the measurement of hormone receptors and of the assessment of the pathological features of the disease in the design of optimal treatments; value and limitations of screening for breast cancer; effects of dietary factors in breast carcinogenesis and the role of nutrition in the management of the disease; application of reconstructive surgery; and irradiation as a possible causative agent for breast cancer.

—Major advances have been recently made through use of bone marrow transplantation as an effective therapeytic approach towards the curative treatment of acute leukemias. These advances will be discussed in terms of the current state of the art, as well as its future projections. Use of interferons in counteracting the limiting complications of bone marrow transplantation therapies that are related to viral infection will be considered.

—Gastrointestinal neoplasias, including pancreatic and hepatic cancer, represent diseases where, apart from the examples of curative surgery, available treatments are still relatively ineffective. Major efforts are directed toward the identification of new treatments. The state of the art in the management of these diseases will be outlined.

—Advances in the management of lung cancer will be discussed from a multidisciplinary point of view. Improvements in the pathological identification of incipient neoplasia and in the assessment of pathological determinants of prognosis will be considered. Smoking and other etiological factors will be assessed.

—Several other types of neoplasias will be considered, in most cases from a multidisciplinary point of view, and the state of the art will be reviewed with emphasis on the special requirements related to the characteristics of these diseases and to the difficulties that need to be overcome toward their definitive management.

—Areas where progress has been matched by controversy are those related to the design and evaluation of clinical trials, and to the classification and staging of various neoplastic diseases. Selected topics in these areas will be extensively discussed and the views endorsed by UICC Programs represented.

—Major advances in radiotherapy will be reviewed particularly as related to the use of high LET particles, the development of effective radiation sensitizers and protectors, patterns of care in radiation oncology, and the therapeutic potential of dose fractionation. Emphasis will also be given to discussions of the therapeutic potential of photoirradiation and hyperthermia.

—Information on the possibility of effecting both cancer causation and therapy through dietary manipulations will be discussed in depth.

—The increasing role of dentistry as an oncological specialty dealing with the management of neoplasias of the oral cavity will be outlined and selective topics reviewed.

—Epidemiology of cancer, with emphasis on those aspects that are related to geographical, environmental and occupational influences on carcinogenesis and the genetic and hormonal factors affecting this process, will be presented.

—The functions and impact of the oncology nurse in different parts of the world will be discussed with emphasis on clinical research.

—The integration of diversified approaches to patient care in the hospice, the socioeconomic aspects involved in the care of the cancer patient, the

team approach to rehabilitation, the psychosocial impact of cancer and the supportive structures of community care versus the role of cancer centers will all be discussed in an effort to give attention to the need for a broad set of approaches focused on the optimal management of cancer.

NCI CONTRACT AWARDS

Title: Maintenance and development of inbred and congenic resistant mouse strains
Contractor: Litton Bionetics, $2,574,583.

Title: Alteration/renovation/maintenance/upgrading projects at Frederick Cancer Research Facility
Contractor: Litton Bionetics, $272,154.

Title: Cancer Communications Network
Contractors: Yale Univ., $598,683; Univ. of Hawaii, $601,543; Michigan Cancer Foundation, $566,221.

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-CB-25505-07

Title: *Maintenance of an animal holding facility and provision of attendant research services*
Deadline: *May 24*

The Div. of Cancer Biology & Diagnosis, NCI, is seeking proposals for a laboratory capable of (1) maintaining a colony of up to 12,000 mice, 40 rabbits, and 500 rats according to National Research Council Standards; (2) breeding special congenic strains of mice not available commercially; (3) providing a technical staff capable of performing bleeding and injections of mice and rabbits, skin grafting of mice, injections and harvesting of mouse ascites tumors, and palpation of mice for detection of tumors; (4) maintaining a freezer bank of serologic products to be used in conjunction with these animals; and (5) transporting animals twice daily between the contract facility and the Clinical Center, NCI. All animals will be supplied by the government.

The successful contractor must be located within a 50-miles radius of the NIH campus. This requirement is set aside 100 percent for small business with a size standard of "its number of employees does not exceed 500 persons."

Contract Specialist: Helen Kelly
RCB, Blair Bldg. Rm. 105
301-427-8877

RFA NIH-NCI-DRCCA-82-2

Title: *The role of natural inhibitors in the prevention of cancer*
Deadline: *Application receipt date: June 15*
Letter of intent receipt date: April 30

The Div. of Resources, Centers & Community Activities, NCI, is interested in supporting studies which are directed at examining the role of several natural inhibitors in the prevention of cancer.

The proposed studies should seek to (1) elucidate further the protective effect of several natural inhibitors in reducing the incidence of various site specific cancers, and (2) lead to a greater understanding of the extent, or action, of several natural inhibitors in the possible cancer prevention processes in humans. Clinical and epidemiological studies are being requested to develop basic information which may be helpful at a later date in decision making with regard to the application of the compounds in clinical trials for chemoprevention.

Chemoprevention refers to the intake or use of chemical agents to interrupt a sequence of events leading to malignancy, or that follow the exposure of an individual to carcinogenic agents which may result in the development of malignancy. A number of natural inhibitors, including vitamin C, beta carotene, vitamin A or its analogs, selenium and alpha tocopherol have been associated, in animals or test systems, with the inhibition of carcinogenesis or have been associated with reduced cancer incidence, in epidemiological investigations. A number of mechanisms have been postulated including increased detoxification of the carcinogen, alteration of metabolism by decreased activation, scavenging of the active molecular species, prevention of the carcinogenic agent from reaching the critical target in the cell, altering permeability or transport, and competitive inhibition.

Because of the numerous reports concerning the effectiveness of these compounds in interfering with carcinogenesis in animals and the many epidemiological studies suggesting a possible negative association of them with cancer incidence, especially in dietary factors and nutrition studies, this RFA is announced.

The purpose of this RFA is to solicit applications from qualified investigators interested in furthering the understanding of the role of beta carotene, vitamin A or analogs, vitamin C, selenium and alpha tocopherol in the prevention of cancer.

The studies envisioned include, but are not necessarily limited to, the following approaches:

1. a. Case Control Studies—utilizing cancer patients and suitable matched controls to study the possible relationship of the designated inhibitors with cancer incidence. Measurement of inhibitor intake or levels should be as direct as possible; indices

not specific for these inhibitors will not be considered for the RFA. These studies may also include investigation of appropriate biological indicators such as serum markers, enzyme levels, etc.

b. Alternate approaches would involve the study of existing data bases with accurate intake information on the designated compounds and the subsequent prospective study of the development of cancer in a defined population.

2. Cohort Studies—involving a population which has consumed varying levels of the designated inhibitors. The investigator would subsequently determine the relative risks of cancer incidence through followup of the population over a number of years. Examination of appropriate biological indicators of intake are also desired.

3. Safety and Adverse Health Effects Studies—Human studies examing the long-term consequence of chronic intake of various compounds to monitor for possible adverse health effects. These studies would be initiated in defined populations identified as having high intake levels of the inhibitors. Approaches might be either case control or cohort studies. Wherever possible, collection and assessment of these data should be incorporated into the studies listed in (1) or (2). Understandings gained through these investigations would also be valuable in examining the feasibility of conducting clinical trials.

4. Risk Reduction Clinical Trials—A fourth category of interest involves populations known to be at very high risk but free of neoplasia, or high risk with identified precursory or precancerous lesions. These studies would require the administration of the designated natural inhibitors in a randomized study with followup to determine the effect of the compound. Proposals involving studies of populations already having neoplastic lesions are not acceptable within the scope of this RFA, but may be submitted in accordance with appropriate grant guidelines and may be of interest to other components of NCI; such proposals would not be responsive to this RFA, however, and would be handled through the usual grant review process.

Several items with regard to the proposal itself are provided as follows:

1. The applicant is encouraged, where germane, to focus attention on a specific target group, or to identify a source of data, and to address the methodological, organizational, and theoretical issues in a detailed manner.

2. The applicant should provide a description of the target or population group chosen and should justify the selection of this group. The group should be specified, where appropriate, by age, sex, race, socio-economic status, dietary customs, education, location, occupational or life style risk factors, and relevancy to a specific cancer problem and to its possible prevention by the designated inhibitors.

3. The applicant should specify the source of data and should document its availability and any required cooperation. If possible, the applicant is encouraged to draw upon existing data rather than collection of extensive original data.

4. Successful grant awardees under this RFA will be required to cooperate with NCI in the evaluation of the role of these designated inhibitors in cancer prevention. A program meeting of one or two days' duration will be held in Bethesda each year of the program in order to review and assess overall progress. Proposals should contain a statement that awardees will participate in this aspect of the program and proposals should include sufficient travel funds within the budget to accommodate expenses for one or two participants at this annual project meeting.

Prospective applicants are asked to submit a one-page letter of intent which includes a very brief synopsis of proposed areas of research and identification of any other participating institutions. This letter should be sent to Dr. Malone at the address below.

The Institute requests such letters only to provide an indication of the number and the scope of applications to be received. The letter of intent is not binding; it will not enter into the review of any proposal subsequently submitted nor is it a necessary requirement for application.

Applications must be submitted on Form PHS 398, the application form for research project grants. Application kits are available at most institutional business offices, or may be obtained from the Div. of Research Grants, NIH. The conventional presentation format and details applicable to regular research grant applications should be followed. The words "Proposal in Response to RFA NIH-NCI-DRCCA-82-2, Studies to Examine the Role of Natural Inhibitors in the Prevention of Cancer" must be typed in bold letters across the top of the face page of the application.

The completed original application and six copies should be sent or delivered to: Div. of Research Grants, National Institutes of Health, Westwood Bldg. Rm. 240, Bethesda, Md. 20205.

A copy of the application should also be sent to Dr. Malone at: Winfred F. Malone, PhD, MPH, Preventive Medicine Branch, Blair Bldg. Rm. 624, NCI, Bethesda, Md. 20205; phone 301-427-8648.

The Cancer Letter _Editor Jerry D. Boyd

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