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## AT LEAST 25 CCOP APPLICANTS SCORE HIGH ENOUGH TO VIRTUALLY ASSURE FUNDING; GEOGRAPHY AN ISSUE

Twenty-five Community Clinical Oncology Program applicants with priority scores almost guaranteeing they will be funded were identified by ***The Cancer Letter*** at press time this week, with another eight whose scores are good enough to qualify them for funding if they are selected on a geographical or other basis.

Those identified by ***The Cancer Letter*** represented only a partial list of the high scoring applications. NCI still had not mailed out summary

*(Continued to page 2)*

*In Brief*

### ROBERT McKENNA NAMED NEW PRESIDENT OF SOCIETY OF SURGICAL ONCOLOGY, HIRAM POLK PRESIDENT ELECT

**ROBERT McKENNA,** Los Angeles surgeon in private practice who is affiliated with the Univ. of Southern California Comprehensive Cancer Center, became president of the Society of Surgical Oncology last week at the organization's 36th annual meeting. Hiram Polk, Univ. of Louisville Medical Center Dept. of Surgery, was named president elect. Victor Dembrow, Miami surgeon in private practice, is the new vice president. Gerald Murphy, director of Roswell Park Memorial Institute and retiring president of the Society, is chairman of the executive council. . . . **SECOND TRIENNIAL** International Award, amounting to about $52,500, will be presented in 1985 to a scientist for "outstanding basic or clinical contributions in oncology." The International Award is made by the Medical Research Centre of Bombay Hospital Trust for outstanding research work in medicine and related fields. Nominations should be sent before March 31, 1984, to H. Nanjundiah, Director, Bombay Hospital Trust, Bombay Hospital Ave, Bombay 400 020, India. . . . **NEW STAFF MEMBERS** in NCI's Div. of Resources, Centers & Community Activities: Phillip Prorok, transferred from the Div. of Cancer Cause & Prevention Biometrics Branch to head the Cancer Screening Section in DRCCA's Biometrics & Operations Branch; Thomas Glynn, from the National Institute on Drug Abuse to become program director for smoking research and control; Ritva Butrum, from the Dept. of Agriculture, to become a program director in the Diet & Cancer Branch. DRCCA Director Peter Greenwald said he is still searching for persons to head the Cancer Control Science Program, the Cancer Centers Branch, the Community Oncology & Rehabilitation Branch, the Occupational Cancer Branch, and the Diet & Cancer Branch. "We also seek several intermediate level scientists both in our extramural and intramural programs," Greenwald told the DRCCA Board of Scientific Counselors. Greenwald may be contacted at NCI, Bldg 31 Rm. 4A32, Bethesda, Md. 20205, phone 301-496-6616.

## TOP 25 (SO FAR) CCOP APPLICANTS LISTED; EIGHT OTHERS ARE CLOSE

*(Continued from page 1)*

statements to all applicants by the end of last week, with the result that many still did not know as late as Tuesday of this week how they fared.

The 25 top scorers so far are, with their scores:

Eastern Maine Medical Center, Bangor, 118; Geisinger Clinic, Danville, Pa., 129; Maine Medical Center, Portland, 133; Grant Hospital, Columbus, Ohio, 148; Allegheny Singer Research Corp., Pittsburgh, 162; Our Lady of Lourdes Hospital, Binghamton, N.Y., 197; St. Raphael Hospital, New Haven, Conn., 184; Good Samaritan Hospital, Los Angeles, 185; Methodist Medical Center of Illinois, Peoria, 194; Flower Hospital, Sylvania, Ohio, 195; Marshfield Medical Foundation, Wisconsin, 197; Mineola, N.Y., 197; Nassau Hospital, New York, 197; St. Francis Regional Medical Center, Wichita, Kansas, 198; St. Vincent Medical Center, Los Angeles, 200; St. John's Mercy Medical Center, St. Louis, 202; Huntington Memorial Hospital, Pasadena, Calif., 204; Menorah Medical Center, Kansas City, Mo., 208; Kettering Medical Center, Ohio, 213; Billings Interhospital Oncology Project, Montana, 215; Beth Israel Hospital, Newark, 220; Ochsner Medical Foundation, New Orleans, 226; Presbyterian St. Luke's Medical Center, Denver, 231; New England Deaconess Hospital, Boston, 232; Kaiser Permanente Hospital, Oakland, 234; and Butterworth Hospital, Grand Rapids, Mich., 235.

Those identified so far with scores perhaps close enough to qualify for funding exceptions, if in fact they are not under the payline, include CCOPs in Memphis (238); Charleston, W. Va. (250); Brooklyn (253); Las Vegas, Nev. (253); Flushing, N.Y. (255); St. Cloud, Minn. (258); Springfield, Ill. (260); and Spartanburg, S.C. (260).

At the meeting last week of the Board of Scientific Counselors of NCI's Div. of Resources, Centers & Community Activities, Jerome Yates, DRCCA associate director for the Centers & Community Oncology Program, said he thought the CCOP review had been "fair and equitable. . . . I can't say enough about the people who worked on this, both those inside NCI and committee members from outside."

One of those from the outside was Virgil Loeb, who chaired one of the three CCOP review committees and who is a member of the DRCCA Board.

"I'm concerned about this matter of geographical spread," Loeb said. "In the review, I'm vividly aware, our emphasis was entirely for potential new information. Were they able to develop the resources? Did they have the patient potential? Is there an opportunity to acquire new scientific information? When I hear you say there will be skipovers to obtain geographical distribution, I become concerned. They weren't reviewed with that in mind. I hope that if you do, you will be awfully good with the justification."

"You know there will be strong justification," Yates said. "Congress is greatly concerned about this. There is a variety of other factors. There is potential in many applications for good cancer control. There is really no difference between 220 and 260 priority scores. We've had calls from some of the cooperative group chairmen (involved as research bases for CCOP applicants) who said they heard some group got such and such score, how in the hell can you do that, they're the best group in the country."

"It's important that geography not be the overriding factor," Loeb insisted.

"It won't be the overriding factor," Greenwald said. "But some states are without representation."

"We're kidding ourselves if we say this is not political," Board member Charles Moertel said. "It is, and for a good political reason. The fact is, there are large areas of the country without access to good care. When some people are 500 miles from good care, that is a good reason. Look at the National Cancer Act, and by God, Congress did say that people should have access to quality care without an overnight stay. As far as the science is concerned, that is something that has already gone before in the research bases. The public need is the most important part of this program."

"There is no question of the need for geographic distribution," Loeb said. "But that could be achieved by taking existing programs and expanding them. This is an attempt to recruit practicing oncologists into clinical research, and expand the patient base."

"I think the review was proper, and properly conducted, for the science," Greenwald said. "It is important to have that. But there have to be some programmatic considerations."

"I'm disturbed by this discussion," Board member Harry Eagle said. "If the primary purpose is to bring patients into the research bases, then scientific review is important. If on the other hand the main purpose is to improve patient care, then geography is important. It is muddying the waters, to take these two objectives and try to doctor the review process and introduce the geographic distribution element."

"Do you really think there is a difference between scores of 220 and 230?" Yates asked.

"I wish you hadn't asked that," Eagle said. "You are striking at the heart of the review process. We will always have differences in scores."

"This is part of the review process," DRCCA Deputy Director Joseph Cullen said. "We have dual review. The first is for the science. The second, by the National Cancer Advisory Board, is for relevance, priority and need, based on our broad mission. That would include geography."

"I'm troubled by the NCAB, on a grant by grant

basis, getting into geography," Eagle said.

The CCOP applications with NCI's recommendations for funding will go to the NCAB May 17.

The funding levels recommended by the review committees in the successful CCOPs identified so far ranged from $50,000 to $100,000 for direct costs, with the median at about $70,000. With indirect costs, it appears that the average total cost will be about $100,000.

Yates told the Board that an agreement had been reached with the research bases on the cost of their part of the program. That has been estimated at about $2.5 million, which would leave $7.5 million for the CCOPs. It appears possible, therefore, that as many as 70-75 CCOPs could be funded.

## DRCCA BOARD AGAIN OKs BREAST CANCER DIET STUDY, AGAIN WITH A CONDITION

The controversial breast cancer low fat diet studies for the second time received conditional approval from the Board of Scientific Counselors of NCI's Div. of Resources, Centers & Community Activities at the Board's meeting last week.

The Board agreed that DRCCA could proceed immediately with issuing requests for application for the studies, but insisted on seeing the results of a smaller compliance feasibility study before the larger studies are implemented. The feasibility study will be completed within a year, DRCCA officials said.

One dietary study would randomize breast cancer patients to normal and low fat diets to determine if the latter reduces recurrence. The other would randomize women at high risk of breast cancer to normal and low fat diets to determine if fat reduction reduces incidence of the disease.

The studies would be conducted for three years, with an additional five years for followup. Cost estimates range as high as $30 million for the entire project.

The DRCCA Board approved the concept of the studies at its January meeting, with the condition that certain questions of some members be considered and brought back to the Board this month. In the interim, the studies were discussed with the Breast Cancer Task Force, some of whose members objected to the concept and to the fact that it had been presented first to the DRCCA Board (***The Cancer Letter,*** April 8).

William DeWys, who heads DRCCA's Prevention Program, presented staff's response to the issues.

The incidence studies will draw entries from women at high risk who participated in the Breast Cancer Detection Demonstration Program. Cooperation of the BCDDP contractors will be required, and some doubt was raised that they would be willing to do so. DeWys said that a survey of 10 contractors found that all 10 were interested in participating.

Are the risk factors predictive? For the purposes of the study, they are familial history (first degree relatives with breast cancer), age at first pregnancy greater than 30, and two or more biopsies for benign breast disease. Women would be considered at high risk with at least two of those risk factors.

DeWys said those risk factors had been selected on the basis of existing literature, but that an analysis is being done from BCDDP data.

The problem of "drop ins" was considered a serious threat to the integrity of the studies by some —that is, members of the control groups will voluntarily reduce fat intake from the normal 40 percent of calories (the study groups will be on 20 percent fat diets).

DeWys said that to combat that possibility, persons already on a low fat diet will be excluded from protocol entry; strategies will be developed to minimize contacts between controls and low fat diet participants; and that without specific instructions, "we doubt that drop-ins will do better than 35 percent fat in the diet."

How about drop outs from the study groups? Board member Charles Moertel argued that most people find it very difficult to modify their diets for an extended period of time, and that too many would drop out of the program to permit valid results.

DeWys said that in the original study plans, a 15 percent drop out rate had been provided for. However, a Canadian study had a drop out rate of 21 percent, so the NCI protocol will be revized to provide for a 20 percent rate.

How will participants be monitored for compliance? Through monitoring of serum cholesterol, and of fat intake as determined by randomly timed 24 hour dietary recall, DeWys said. Also, a lead in feasibility study on documenting compliance will be undertaken, and it will be the results of this study that the Board will see before permitting the overall studies to proceed.

The strategy to promote compliance will include selection of a study population having a high level of interest and concern; individual assessment—personal plan based on dietary preferences and personal instruction; written suggestions for shopping, recipes, menus; cooking demonstrations for principles of preparing food, and to introduce new methods; and close contact on followup through randomly timed phone calls and frequent visits to the center.

Some Breast Cancer Task Force members were concerned about a possible confounding effect of a reduced caloric intake. The percentages 40 and 20 represent the percentage of calories derived from fat. It would be possible to reduce that percentage significantly without reducing the total caloric intake, but it is more likely that some reduction in overall calories will occur.

DeWys acknowledged that some confounding will take place, but suggested it will be "additive" to the low fat effect. "We will not be able to dissect reduced calories from reduced fat, but in any case we are testing a strategy," that is, whether incidence and recurrence rates can be reduced through a low fat diet which incidentally also may be lower in calories.

DeWys said the Breast Cancer Task Force is satisfied now about the program. After presenting the same response to the concerns which he gave to the Board to BCTF Chairman Moyses Szklo, DeWys said Szklo said, "You've answered all our concerns, and I think you should go ahead with the trials."

Szklo, however, did not agree with that interpretation of his conversation with DeWys. "This is an exaggeration of what I said," Szklo told ***The Cancer Letter.*** "I don't want to get into an argument about what I said, but what I felt was that I enjoyed the way he responded. I told him that the study addresses a terribly important problem. He has made an effort to answer some of our concerns. But he did not answer some other concerns."

Szklo suggested that a third arm be added to the studies, with its entrants on a weight losing diet without reduction in fat percentage. That would overcome the confounding effect mentioned above, but DeWys said, "I can't envision how that could be done in human studies," since participants in the two modified diet groups would have to be matched pound for pound.

Szklo also said he would like to see more case control studies undertaken before the randomized trial is started. DeWys' reaction was that there has already been a moderate number of case control studies reported and that adding more would not provide that much more information.

Board member Leonard Derogatis objected to the 20 percent allowed for drop outs, contending that it is not high enough. Some of the breast cancer patients will be taking chemotherapy and may find it even more difficult to modify eating habits during that stressful period, he said. DeWys said he would accept a higher figure, and Derogatis agreed to suggest one after studying the issue further.

Board member Ernst Wynder said, "One thing I'm certain of is that this will never succeed unless there is great involvement of physicians." DeWys agreed "we'll make sure of that."

"I still have concerns about both of these studies," Moertel said. "The Board is being asked to approve specific protocols, in contrast to putting out a call for investigator initiated proposals. I don't believe this Board was established with the expertise to judge cancer treatment protocols of this kind. The Breast Cancer Task Force raised serious objections. They felt this should have been brought to them first. They also had concerns about the protocols. . . .

"If you're going to impose this on existing groups, and I presume this must include cooperative groups, some of them will have physicians who will watch it closely. Others will be too busy, perhaps with no enthusiasm. You will have numbers of ineligible patients, unevaluable patients, canceled entries. There sometimes are biases on why patients are thrown out of studies. The problems cooperative groups have with protocol violations and cancelations will be magnified. . . .

"You can't separate those groups. These gals get together to talk all the time. You will have a certain number of health motivated individuals who will adopt the low fat diet. You get all of these things together, and you're talking about a $30 million program. Wow! When you consider the other priorities of the National Cancer Program, that's not an appropriate expenditure for this division."

Board member Jerome DeCoss said, "While I agree with your apprehensions, I think Bill will try to protect for that with the feasibility study. The question is important enough, and the possibility for success high enough, to merit the feasibility study. Will you accept that strategy?"

"The question is if it is feasible to get middle aged, obese women to accept a diet. I will vote for the feasibility study. Once that's established, then come back and ask for a $30 million study."

Board member David Eddy asked, "Suppose the feasibility study is negative? Would we then not recommend a low fat diet? Would we wait for positive studies? I hope that 10 years from now we're not saying, 'We should have done that study 10 years ago.'"

DeWys pointed out that each of the trials will cost about $15 million, and "the Div. of Cancer Treatment spends $15 million a year on breast cancer. We're talking about $15 million over five years."

DeWys said that not all members of all cooperative groups have high rates of ineligibility. "There are many who do. There are usually one or two groups that pull the average down. The existing cooperative groups are stuck with the baggage of the poor performers. We can be selective with this."

DRCCA Director Peter Greenwald argued that the information needed from the trials could "impact the national diet, the food supply. Billions of dollars are involved. . . . Would a few more studies make any difference? I don't think so. It is a major problem and there is a prospect for major gains. We have to get started."

"Maybe the randomized trial is a shiboleth," DeCosse said. "There could be better ways. Randomize cities, or families."

"I agree it is an important problem," Moertel said. "But this has so many obvious problems that it could be defeating exactly what you wish to accomplish. It is doomed to failure by those problems."

"What difference would this particular information make?" Board Chairman Lester Breslow asked. "I don't think this or any other single study would make much difference." Referring to the problem of smoking, he said, "We may need a whole series of studies, although maybe not as expensive as this."

"Don't underestimate the importance," Greenwald said, suggesting that government agencies, private groups interested in nutrition, and industry would use it.

"Those groups will hang you alive if you do not have sound data," Moertel said. "There never was a randomized trial on smoking, but a large number of people have been convinced."

But Greenwald pointed that that Wynder did his landmark smoking study which was the first to provide scientific evidence of the link between tobacco and cancer in 1950, "and we still have not convinced enough people."

"We're trying to establish if low fat makes a difference," Moertel said.

"That's exactly what the study is designed to do," Greenwald answered.

"I believe that next to cigarette smoking, dietary fat is the largest preventable cause of cancer," Wynder said.

Board member Kaye Kilburn asked, "What's the alternative? I don't think there is a suitable alternative now. Here is a place, where we can take the predominant cancer in women and move from retrospective analysis to a prospective study, and move forward. What's been spent on breast cancer therapy, of public funds, is five times this amount. When you look at the public cost, that is magnified. Let's not be sitting around a table in five years and say, 'Gee, it would have been nice to have had a trial.' For God's sake, let's get on with it."

"Maybe it won't work, but if it should, we will have made a major contribution, much more than we've had from therapy," Board member Saxon Graham said.

"This looks like the argument that since kids put so many billions into TV games, why not X amount into cancer. The point is, is this good science? My concern is that it would hurt prevention. It is an important issue, being addressed in a bad way, because a clinical randomized trial is not feasible."

Moertel suggested that no further steps be taken to proceed with the study until the compliance feasibility study has been completed. However, Greenwald said that it would be difficult to split the feasibility study from the rest of the project and that to delay the RFAs now would result in unnecessary delays later. He suggested that the Board approve the concept now with the proviso that it will have the privilege of saying "go or no go" after the feasibility study has been completed.

Moertel, Breslow, and Board member Virgil Loeb agreed with that approach, and the Board approved it unanimously.

## NCI, NIAID ANNOUNCE FOUR AWARDS TOTALING $250,000 FOR AIDS RESEARCH

NCI and the National Institute of Allergy & Infectious Diseases announced awards totaling $250,000 in direct costs to fund four new studies on acquired immune deficiency syndrome (AIDS).

The projects to be funded by NCI are to: John Hughes, Children's Hospital, Columbus Ohio, $46,241 first year funding; and Martin Hirsch, Massachusetts General Hospital, $97,983. NIAID is funding Walter Hughes, St. Jude Children's Research Hospital, $62,332, and Pearl Ma, St. Vincent's Hospital & Medical Center, New York, $39,165.

## ONLY THREE OF 28 CCRU, CCSP PROPOSALS APPROVED, BUT DRCCA WILL TRY AGAIN

Despite some "quite discouraging" results of the first round of competition for the major new Cancer Control Program initiatives—Cancer Control Research Units and Cancer Control Science Program—the Board of Scientific Counselors of the Div. of Resources, Centers & Community Activities gave concept approval to a second round of competition for the two programs.

DRCCA hopes this time to award five grants for each program, with CCRUs to be funded at an estimated $700,000 each and CCSPs at an estimated $400,000 each. The CCSPs this time will be program projects instead of the P50 grants.

Carlos Caban, program director for the two projects which are administered by the Cancer Control Applications Branch, told the Board that only three of 28 applicants for CCRU and CCSP grants made it through the merit review approval process. Another was returned for a new site visit.

All three of those approved--two CCSP applications and one CCRU—will be recommended to the National Cancer Advisory Board next week for funding.

Only 32 projects of the 142 proposed in the 28 applications were approved, a 23 percent approval rate. Only seven of the 30 proposed phase IV studies were approved. There is a total of 11 projects in the three approved applications.

"All of the investigators put forth major efforts in responding to the CCRU and CCSP announcements," Caban said. "As you can see, these results are quite discouraging."

Eight of the 28 applications were CCRUs. Another three CCSP applications were submitted for the second deadline and are currently in the review cycle. An additional eight institutions submitted letters of intent to submit applications but did not do so for various reasons.

Among the positive aspects of the first round,

Caban said, was the fact that 85-90 percent of project investigators and PIs were newly recruited to cancer control research; about 25 percent of them had other R01 support. "They are now trying to apply their knowledge and experience to cancer control intervention problems."

A total of 142 research projects and approximately 70 developmental projects were proposed by these new investigators. This is an average of five projects per application, with a range from three to seven projects. "It should be noted that recent NCI program projects have averaged about eight projects per application," Caban said.

Caban said that most of the disapprovals were due to major deficiencies in the proposed projects, the result, he felt, of the fact that investigators were new to cancer control. With the help of DRCCA staff and guidance from remarks of reviewers, they should do better the next time around, Caban said. Substantial revisions in the two programs have been made and will be spelled out in the RFAs.

"We have strengthened the CCRU by restating the goal to include more focused programmatic or problem oriented research," Caban said. "We see the CCRU as being both a program and a training resource for the Cancer Control Program. As stated in the written concept, the CCRUs should develop areas of special expertise which are compatible with their resources and research interests. They will not be required to develop a comprehensive approach to cancer control research."

Additions to the CCRU concept include:

—Program and problem oriented research focus in one or more areas.

—Requirement for two defined population studies initially, (instead of the original requirement for three), and the requirement for three at renewal time.

—Adding applied epidemiology studies, which are often needed before a full-blown research project can be formulated.

—Allowing applied epidemiology and developmental studies to make up 20 percent of the application direct costs.

—Establishing an option for cancer control research training programs.

The major deletion is that a chemoprevention study will not substitute for a defined population study in meeting the minimum criteria.

Application submission dates for this RFA probably will be Oct. 1 and Feb. 1. Letters of intent will be requested. Grants may be from three to five years.

Cancer Control Science program projects will become traditional program project grants, with one specific central theme to which each proposed project relates and contributes.

"Many research problems in cancer control require a multidisciplinary approach," Caban said. "The program project approach is ideal for stimulating this approach, and is complementary to the traditional R01 project grant. Both types of grants are important in building a solid research base in cancer control science.

"The specific program area or major cancer problem for the program project will be chosen by the investigators. Interrelated projects may be from phases II through V and should be expected to result in a greater contribution to the stated program goals than if each project were pursued individually.

"Program project grants may include research projects, a small organizational and administrative structure, and core components. There is no minimum number of projects required. No developmental funds are allowed."

Application receipt dates probably will be Oct. 1 and Feb. 1. Letters of intent will be requested. Applicants may request from three to five years support.

The staff narrative describing the CCRU concept and justifying it:

The goal is to establish Cancer Control Research Units which will plan and implement cancer control defined population research studies in programmatic areas such as prevention, management, or major cancer control problems. The focused programmatic research shall include innovative approaches to reducing cancer incidence, morbidity and/or mortality, and be generalizable to larger populations. The CCRUs will serve as program and training resources for the cancer control research program of the National Cancer program.

Additional Cancer Control Research Units will be established in response to the critical need for special multidisciplinary centers of excellence which will focus on cancer control research studies in general program areas such as cancer prevention, management, or major cancer control problems. The intent is for CCRUs to develop areas of special expertise which are compatible with their resources and research intents. It is not necessary for a CCRU to develop a comprehensive approach to cancer control research.

The Cancer Control Research Unit will identify its major programmatic theme areas, the resources needed to support the long term research effort, and the potential impact of the

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

**The dollar estimates with each concept review brought before the various boards of scientific counselors are not intended to represent maximum or exact amounts which will be spent on those projects. They are intended only as guides for board members to help in determining the value of the projects in relation to resources available to the entire program or division. Responses should be based on the workscope and description of goals and methods included in the RFPs (contracts) and RFAs (grants and cooperative agreements). Availability of RFPs and RFAs will be announced when the Institute is ready to release them.**

proposed research effort in addressing the stated cancer problems. These CCRUs will require long term support, multidisciplinary participation and collaboration, and access to defined populations so that the population impact of any cancer control activities can be measured.

The required components of a CCRU will include:

- A rationale for the CCRU in terms of the cancer control problems which will be investigated.
- An experienced investigator/administrator as CCRU director.
- A multidisciplinary cancer control research team of qualified investigators, and an underlying research base.
- At least three peer reviewed research projects, of which two must be defined population studies.
- Organizational, administrative and institutional procedures, commitments and support.

Optional components of a CCRU are:

- Limited developmental or research projects, including applied epidemiology. Investigators new to cancer control research may use developmental projects to do preliminary research before submitting regular research project grant applications.
- Shared resources cores in support of two or more projects.
- An option to establish cancer control research training programs, including field involvement, and to seek peer reviewed support through NCI training project grants.

Three projects must be approved as part of the application before the CCRU application will be considered for funding based on its priority score. The CCRU may request support for three to five years, with the opportunity for renewal. At renewal time, three defined population studies will be required.

Applied epidemiology studies refer to epidemiologic, planning and survey studies aimed at developing cancer control interventions. The investigator should already have in mind some idea of a cancer control problem or a hypothesis regarding an intervention. Such studies, for example, might provide more information about the population, or other information vital to the more specific formulation of cancer control intervention studies. These would be cancer control phase I and II studies.

The investigators should describe how these studies will lead to an intervention. Preference will be given to defined population applied epidemiology. Follow through on these studies to research on cancer control interventions will be considered in the review of renewal applications. Up to 20 percent of the direct costs of the CCRU application may be devoted to the developmental and applied epidemiology studies.

It is believed that, at this time, a number of institutions or organizations in the United States have the "critical mass" of resources and qualified personnel to become cancer control research units as described above, but lack a clear mandate and method of support. The concept of Cancer Control Research Unit is being put forth to address this critical need.

The narrative describing and justifying the CCSP concept:

The goal is to establish Cancer Control Science Program Projects which will plan and implement programmatically focused cancer control research studies. The research shall include innovative approaches with protential for reducing cancer incidence, morbidity and/or mortality, and for generalizability to larger populations.

Program projects in cancer control science will be established in response to the critical need for programmatically focused multidisciplinary research aimed at major cancer control research problems.

The program projects will identify one specific central theme (e.g., a program area or major cancer problem) which will be investigated within the general areas of the NCI Cancer Control Program. A thematically integrated group of projects from cancer control research phases II and V should be proposed, which would be expected to result in a greater contribution to the stated program goals than if each project were pursued individually. These program projects will require long term support and multidisciplinary participation and collaboration.

Program project applications should follow the "Guidelines for the Program Project Grant of the NCI," including the following stated criteria for a program project grant:

1. There must be a central theme to which each project relates and contributes.
2. Each component project must stand on its independent merit, as well as complement or contribute to the other projects.
3. All investigators must contribute to, share in, and relate to the common program theme.
4. A mechanism for the interrelation and communication of the ideas and results of all participants must be demonstrated.

The components of the program project include research projects, an organizational and administrative structre, and core components. No developmental funds are allowed.

The NCI Cancer Control Program has recently clarified its general research program. New grant guidelines are available for investigator initiated project grants (the traditional R01 grant). In addition, many research problems in cancer control require a multidisciplinary approach covering a broader spectrum of disciplines including basic, epidemiologic, biostatistical, clinical, behavioral, health services research and applied research sciences. The program project approach is ideal for stimulating this critical multidisciplinary approach to cancer control research problems, and is complementary to the traditional R01 project grant route. Both types of grants are important in building a solid research base in cancer control science.

## CHEMOPREVENTIVE PHASE I, PRECLINICAL TOXICOLOGY, EFFICACY STUDIES OKAYED

The DRCCA Board of Scientific Counselors gave concept approval for phase I clinical trials of new chemopreventive agents through extramural master agreement-task order contracts and intramural studies at the NIH Clinical Center.

DRCCA staff estimated that the extramural phase I trials would cost about $75,000 per agent and tentatively budgeted for eight such tests a year. An RFP will be issued inviting institutions to compete for recognition as one of the master agreement holders. As agents become ready for phase I testing, they will be competed only among those master agreement holders. Staff estimated that four master agreements would be established, with each testing four agents.

Staff narrative:

The specific objectives of the contracts resulting from this RFP will be to provide the Prevention Program with the phase I clinical evaluation of investigational agents which are developed through the chemoprevention linear array and are sponsored to FDA under an IND held by DRCCA.

The objective of phase I studies is to provide the parameters and characteristics of toxicity, the maximally tolerated or safely delivered dose, and basic clinical pharmacokinetics

of agents emerging from the NCI chemopreventive agent development program.

Offerors will be asked to submit, in their technical proposals, a proposed master protocol for phase I studies detialing all aspects of the study except those determined by the specific agents. The final protocols of all contractors funded will use common definitions and criteria for toxicity as indicated by NCI. Specific elements of a master protocol would include: Criteria for subject selection and eligibility; approach to the selection of an initial dose and schedule and escalation levels; number of subjects at each level and subject re-entry at another dose escalation level; criteria which define an evaluable course; frequency and methods for assessing toxicity; objective definition of the maximally tolerated dose; toxicity criteria for each organ system; patient report form formats; the format for subject informed consent; and general approach to complementary pharmacokinetic studies.

Contractors will develop and perform specific phase I protocols at the direction of NCI. Such protocols must be approved by the contractor's investigational review board and contain an informed consent form specific for the investigational agent. All specific protocols will be reviewed by the DRCCA Safety and Protocol Review Committee, and will then be sponsored by the NCI under an IND in accordance with FDA regulations.

Contractors will be expected to perform at least one study per year on an average minimum of 25 fully evaluable subjects per study. Monthly updates of subject data will be submitted to the Chemoprevention Monitoring System. The contractor will produce and submit a final report on the results of each study along with the individual study report form for each subject included in the study.

The intramural portion of the concept approved by the Board was presented in two parts, one for the phase I testing of synthetic retinoids, the second for other chemopreventive agents. Staff estimated the annual cost of testing retinoids to be $55,000 per agent, with two agents to be tested a year; for other agents, the cost of testing would be the same for each, but estimating only one per year to be tested. The program was approved for three years.

The Board also approved the concept for preclinical toxicology of chemopreventive agents, after modifying the concept to change the mechanism from contracts to master agreements.

The budget for preclinical toxicology was estimated at $800,000 a year, to cover two contractors. However, that testing can be very expensive, with each agent costing as much as $400,000, depending on the extent of studies required by FDA.

The narrative:

Prior to approval of investigational new drug applications by FDA, preclinical toxicological information must be provided. The primary purpose of this project is to develop the quantitative information required prior to initiating human trials at a safe dose and to provide the qualitative toxicological information to indicate that there is no life threatening irreversible toxicity that would preclude entry of the agents into phase I clinical trials.

The basic objectives of this project will be to evaluate the acute, subacute/subchronic and chronic toxicity of designated agents. These studies will be performed in animals (rodents and dogs) and should include conventional short term studies, lifetime studies in rodents, and multigeneration teratogenicity studies. The agents would be given by either oral or intraperitoneal routes.

All substances may not need to undergo all phases of testing. Types of studies and endpoints would be determined by the NCI project officer in cooperation with principal investigator.

The Board also approved the concept of contract supported preclinical efficacy studies of chemopreventive agents in animals.

Staff had estimated that two awards would be made, at $400,000 per year each. However, Board member Harry Eagle suggested that the work should be opened to more institutions, and DeWys agreed.

The narrative:

Various in vitro techniques are being utilized to determine the efficacy of chemopreventive agents. There is now a need for the testing of the efficacy of these compounds in long term animal studies and the development and refinement of appropriate animal models. In the case of retinoids, animal models for bladder, breast and skin cancer are available. Models for pancreatic, prostate, esophageal, and colon carcinogenesis require further development. At present there is also a need for the study of pharmacokinetic principles for the selection of new agents in the prevention of cancer at specific target sites. Prior to selection of compounds for further evaluation in human clinical trials there is a need for study of their efficacy in animal models.

A number of organ specific animal models now exist in which initiation may be rapidly completed in a defined period by the administration of a small number of doses (even a single dose) of carcinogen. One then can study the effect of potential chemopreventive agents on blocking further promotion in the progression of carcinogenesis during the latent period when cells are still in a pre-neoplastic state and before invasive malignancy is histologically detectable.

This approach has been used in prevention of experimental bladder and breast cancer. Bladder models include: 1) Wistar-Lewis rats dosed with N-Methyl N-nitrosourea, 2) Fischer rats dosed with N-butyl-N-4 hydroxybutylnitrosamine (HO-BBN), 3) C57 BL/6 mice dosed orally with HO-BBN and 4) $B_6D2F1$ mice dosed with HO-BBN. These different animal models provide a spectrum of both transitional and squamous cell carcinoma of bladder that closely resembles various stages of human disease.

Breast cancer is also a disease characterized by a prolonged series of premalignant epithelial changes before the development of invasive malignancy. For example, a number of models is available including those employing the carcinogens, DMBA and N-Methyl-N-Nitrosourea. Models for skin papillomas and carcinomas in mice are also available.

Models to prevent epithelial carcinogenesis at other organ sites have not yet given as definite results as the studies on bladder, breast and skin. Animal models for the prevention of pancreatic, prostatic, esophageal and colon carcinogenesis will require further development and refinement.

**The Cancer Letter** _Editor Jerry D. Boyd

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