THE CANCER LETTER

Vol. 18 No. 28
July 10, 1992

Price $215 Per Year US, Canada
$240 Per Year Elsewhere

P.O. Box 15189 Washington, D.C. 20003 Telephone 202-543-7665

DCT Advisors Approve $22 Mil. Set Aside For Interactive R01s In Systemic Therapies

Advisors to NCI's Div. of Cancer Treatment have given concept approval to a new grant program that would set aside as much as $22 million over the next four years to fund "interactive" research project grants for clinical studies of innovative systemic therapies.

The proposed Request for Applications is part of an attempt by the Institute to meet a Congressional requirement on the number of grants that must be funded. The grants target put the more costly program

(Continued to page 2)

In Brief

NCI Awards 4 Contracts For Enrichment Program; Dana-Farber Names Breast Center Leadership

CONTRACTS have been awarded to four institutions that will run regional versions of NCI's popular Science Enrichment Program, sponsored by the Div. of Cancer Prevention & Control. Two-year contracts were awarded to the Univ. of Massachusetts ($957,340), Univ. of Kentucky Research Foundation ($690,662), Univ. of Southern California ($576,272), and the American Indian Science & Engineering Society, ($293,962). The contracts include an option for an additional two-year period. The proposals were put through a rush review process to enable the institutions to provide the enrichment program to minority and underserved youth this summer. . . . **DANA-FARBER** Cancer Institute has named three co-directors of its Breast Evaluation Center to replace clinical director **Craig Henderson**, who moved to Univ. of California (San Francisco). **Daniel Hays**, associate physician at Brigham and Women's Hospital, was named medical director; **Timothy Eberlein**, chief of surgical oncology at Brigham and Women's Hospital, was named surgical director; and **Jay Harris**, chief of radiation oncology at Beth Israel Hospital, was named radiation oncology director. . . . **"CANCER PRACTICE,"** a "multidisciplinary journal of cancer care," will join the stable of American Cancer Society publications in May, 1993. It will be a companion journal to "Cancer," both published for ACS by J.B. Lippincott Co. **Genevieve Foley**, director of nursing practice at Memorial Sloan-Kettering Cancer Center, is the editor. Charter subscription is $35. Information on manuscript submission may be obtained from J.B. Lippincott, Journals Dept: SK, 227 E. Washington Sq., Philadelphia 19106. . . . **INTERNATIONAL UNION** Against Cancer (UICC) has changed its phone and fax numbers. New phone no. is (41-22)320-1811; fax (41-22)320-1810. Address remains 3 rue du Conseil-General, 1205 Geneva, Switzerland.

DCT Advisors Set Aside $22 Million For Interactive R01s In Next 4 Years

(Continued from page 1)

project (P01) grants, made up of several separate projects, at a severe disadvantage, since a P01 counts as only one grant. NCI last year devised the interactive mechanism, which links at least three R01s, to begin substituting for P01s. The interactive R01s count as separate grants.

However, there were only three sets of applications submitted for the Feb. 1 deadline to the Institute-wide interactive R01 program announcement issued earlier this year (**The Cancer Letter,** Jan. 17). Each set had to have at least three individual R01s, but the actual number of applications submitted was not available. According to NCI staff, there were "a number" of applications for the June 1 deadline, but it is still too early to determine exactly how many were submitted. One problem has been that sometimes the applications are not entered into the NIH computer system as interactive R01s.

The "biggest problem" with the generic interactive R01 program announcement has been the lack of a single study section to review all applications, according to Cancer Therapy Evaluation Program Director Michael Friedman. The applications submitted as a package are split among several different study sections. "There is no sense of the unity of the projects. That is almost sure to result in not having an overall view of the project and in not funding the project," he said to **The Cancer Letter.**

Thus, NCI divisions, with approval of their advisory boards, have made plans to set aside money from the research project grants budget to fund interactive R01s addressing specific needs.

"The advantage of the RFA is that there is a single study section, which can see the whole project and its merits," Friedman said. "It is somewhat similar to the way P01s are reviewed. We think that having interactive R01s submitted outside of the RFA is not likely to result in funding the whole project."

"I'm wildly enthusiastic about this concept," said DCT Board of Scientific Counselors Chairman Ronald Levy. "It's a great way to deal with the P01 problem."

Following is the concept statement, approved unanimously at the board's meeting last month:

Interactive R01s for clinical studies of innovative systemic therapies. Proposed RFA, $4 million per year in FY 1993, and $6 million per year in FY94-96, for a total of $22 million. Cancer Therapy Evaluation Program.

Investigator-initiated grant support is by far the largest single entity in the NCI research budget. NCI utilizes a range of funding mechanisms to support clinical research efforts of differing scale and scope. For the conduct of large scale, multi-institutional clinical trials, the Cancer Therapy Evaluation Program has established a unique program of integrated national networks of clinical investigators and institutions (Clinical Trials Cooperative Groups (CTCGs). The efforts of these cooperative groups involve a collegial interaction between investigators and NCI professional staff and are supported through cooperative agreements (U10 awards) under a separate line item in NCI's budget.

The primary goal of these trials is the definitive evaluation of clinical treatment programs. These groups have limited involvement with pilot studies and ancillary laboratory studies that bridge the gap between the laboratory and the clinic. Currently these clinical studies are supported by grants (R01, P01, and U01 awards) under the research project grant category. This smaller scale clinical research is usually done within single institutions or in small consortia of institutions interested in a particular area of therapeutic investigation. These investigator initiated mechanisms support early clinical development of new therapeutic agents and treatment modalities. They support pharmacokinetic studies, studies of mechanisms of action and resistance of therapeutic agents, and all types of clinical correlative studies. This effort is the essence of translational research which brings the basic science to the bedside and provides leads for definitive treatment trials performed in CTCGs.

An unprecedented number of new therapeutic agents is ready for evaluation in pilot clinical studies at this time. In addition, insights into the biologic function and clinical relevance of growth factors, genes that promote and suppress neoplasia; mechanisms of treatment sensitivity and resistance; and function of the immune system provide important new clinical research opportunities for investigators. NCI is interested in expanding support for clinical research. Historically, investigators engaged in traditional research have relied heavily on the P01 grant mechanism for support. Support for clinical research through the P01 grant mechanism has decreased in recent years and a new interactive R01 mechanism has been proposed as an alternative. This mechanism is not meant to replace the P01 mechanism.

The interactive research project grant (IRPG) is defined as three or more investigator-initiated research grant proposals which are reviewed for independent merit but which share a theme(s) or resource(s) and which require concurrent funding to maximize the effectiveness of the resource or to allow maximal creative interaction among researchers. Applicants will benefit from use of the IRPG mechanism by establishing a larger framework of reference for the proposed work, by facilitating formal collaborations tailored to achieving research objectives, by

THE CANCER LETTER

Editor: **Kirsten Boyd Goldberg**
Founder & Contributing Editor: **Jerry D. Boyd**
Associate Editor: **Paul Goldberg**

PO Box 15189, Washington, DC 20003
Tel: (202) 543-7665 Fax: (202) 543-6879

Subscription rate $215 per year North America, $240 elsewhere. ISSN 0096-3917. Published 48 times a year by The Cancer Letter Inc., also publisher of The Clinical Cancer Letter.

providing a record of independently acquired awards credited to each funded investigator, and by allowing retention of research autonomy by the named principal investigator on each of the interactive grants.

This proposed RFA will solicit IRPG applications to perform research projects designed to conduct clinical studies investigating promising therapeutic approaches in a single tumor type or to develop new treatment strategies focused on a single class of novel compounds or a mechanism of action. The projects must have therapeutic intent involving systemic therapies and a minimum of two clinical trials should be proposed. The clinical trials may or may not have ancillary correlative laboratory studies and be located within one R01 application or in separate R01 applications. The total cost requested for each IRPG (consisting of three or more R01s) is limited to $750,000 per year. Thus it is anticipated that six IRPGs will be funded in FY 1993. In FY 1993 this RFA will be re-advertised and an additional three IRPGs will be funded in FY 1994.

Support will be provided to institutions with established clinical, laboratory, and statistical resources. Some examples of clinical research areas that would qualify are: (1) drug development studies leading to new clinical trials; (2) new systemic therapies utilizing drugs and biologics as single agents or in combination with other modalities; (3) studies to elucidate the mechanism of action of therapeutic agents alone or in combination; and (4) clinical correlative studies designed to improve therapeutic approaches. Investigators are not limited to the above examples of potential studies. NCI encourages investigators to propose other scientific approaches that suit the interactive R01 mechanism and the requirements of this proposed RFA.

Another NIH Authorization Attempt Includes Provision For Breast Cancer

Expanded programs for breast and gynecological cancers are part of the new Congressional attempt at legislation authorizing the National Institutes of Health.

The new bills, introduced by Rep. Henry Waxman (D-CA) and Sen. Edward Kennedy (D-MA), provide for $300 million to be spent by NCI on breast and gynecological cancer research. These provisions survived from the previous authorization bill, which was recently vetoed by the President. Congress was over a dozen votes short of the two-thirds majority needed to override the veto. Bush said the legislation that authorized $5.4 billion for medical research was too costly and that research using fetal tissue had "potential for promoting and legitimatizing abortion."

While the attempt to end the ban on fetal tissue research was the crucial stumbling block for the original legislation, the provision for new programs in breast and gynecological cancer research can be taken as an indication of the endurance of Congressional backing for these programs.

It is not likely that increased appropriations would accompany the new mandate, according to Capitol Hill sources. That could mean that existing NCI programs would have to be reshuffled.

Both the House and Senate versions of the new authorization bill contain provisions for $225 million for research, treatment and prevention of breast cancer and $75 million for similar programs in gynecological cancers.

Also, both bills call for spending an additional $72 million on prostate cancer.

The breast and gynecological cancer initiatives were placed in the legislation as a result of lobbying by Women's Congressional Caucus and the Breast Cancer Coalition, an umbrella group of over 140 grassroots organizations.

The National Coalition for Cancer Research opposes any shift in funds that could occur as a result of starting the new programs. NCCR, a coalition of 16 professional societies and lay organizations, wants new funds to accompany the new programs.

The future of the mandate and its effect on NCI's budget will become clearer later this month, when the budget is reported to the House Appropriations Committee. The Institute's FY1993 budget was marked up by the Labor, HHS & Education subcommittee shortly before the July 4 recess, but the results are being kept under wraps by the subcommittee.

The Kennedy and Waxman NIH authorization bills are also expected to go to markup later this month.

As a compromise on fetal tissue research, the new authorization bills would require researchers to obtain materials from "fetal tissue banks" that would store tissue obtained by means other than elective abortions. However, if the materials are not available at tissue banks, researchers would be free to look elsewhere.

In a related matter, political support for expanded research in breast and gynecological cancers is reflected in the 1992 Democratic platform, which pledges to make "ending the breast cancer epidemic a major priority, and expand research on breast, cervical and ovarian cancer." The platform also calls for expansion of medical research and universal access to affordable health care.

DCT Advisors Ok Grant Programs To Expand Trials Of New Agents

NCI advisors have given concept approval to two new grant programs designed to expand phase 1 and 2 clinical trials of new anticancer agents.

The Div. of Cancer Treatment Board of Scientific Counselors agreed to set aside $16 million over the next four years to fund 16 to 18 cooperative agreements (U01s) to institutions to conduct up to 18 phase 1 or 14 phase 2 trials each per year.

The grants are intended to augment existing contracts for the conduct of phase 1 and 2 trials. "Our interests are not well served by having limited phase 1 and 2 activity when there are so many interesting research questions," Cancer Therapy Evaluation Program Director Michael Friedman said. "I conservatively estimate 27 new candidate compounds will be available for phase 1 study in the next year or year and a half."

Following are excerpts of the concept statements:

Phase 1 trials of new anticancer agents. Proposed RFA (cooperative agreement), first year award $2 million, four years ($8 million total), six to eight awards. Cancer Therapy Evaluation Program.

Phase I clinical trials have as their objectives the characterization of drug toxicity, maximally tolerated dose, pharmacokinetic, and biological effects (pharmacodynamics) of drugs. These anticancer agents have traditionally been obtained either from the NCI drug development program or through collaborative drug development agreements with the pharmaceutical industry. Recent advances in understanding of the pathobiology of malignancy are leading to the development of a wide range of novel anticancer therapeutic agents that require phase 1 testing.

The increasing number of promising new agents with novel mechanisms of action and the large number of institutions both capable of and interested in conducting phase I clinical trials of cancer therapies make it desirable to expand NCI grant support in this area. The need for increased resources for clinical development of a wide range of novel anticancer agents has led to this request for cooperative agreements to establish the pharmacological and initial clinical characteristics of these agents. Institutions responding to this proposed RFA should be able to perform phase I trials and to establish the pharmacological characteristics, in parallel with biochemical and other appropriate biological studies, of the effects of these agents on cancer cells and normal tissues. Applicants will be funded via cooperative agreements. The agents to be studied in these trials will be those that are of mutual interest to the investigators and NCI.

NCI will invite applications from institutions interested in performing phase I trials of promising anticancer agents in patients with cancer refractory to currently available therapy and in conducting laboratory studies relevant to the clinical development of the agents. Scientific approaches should reflect the creativity and capabilities of investigators. Institutions submitting applications must have the following capabilities: (1) documented numbers of eligible patients with a history of adequate accrual to perform phase I trials; (2) laboratory support within the institution to perform pharmacokinetic studies of cytotoxic, differentiation inducing, and targeted anticancer agents, including monitoring of metabolites and intracellular products when appropriate, or other relevant laboratory correlative studies; (3) laboratory support within the institution to measure relevant indicators of pharmacodynamic or biologic response (e.g., changes in signal transduction pathways, induction or suppression of specific gene function, other indications of differentiation induction, or induction of apoptosis); and (4) adequate central data collection and processing capabilities as well as biostatistical expertise.

It is anticipated that six to eight institutions will be supported on this RFA, which will provide the capability of performing a total of 12 to 18 phase I trials annually.

NCI will provide anticancer agents, when appropriate, assistance in the nature of information regarding particular agents, NCI priorities with regard to drug development, and updates of ongoing efforts elsewhere in the scientific community, as well as oversight, through the protocol review process, of methodology, feasibility, patient safety, and adherence to regulatory requirements mandated by NCI's role as a drug sponsor.

Phase 2 trials of new anticancer agents. Proposed RFA (cooperative agreement), first year award $2 million, four years, ($8 million total) six to eight awards. Cancer Therapy Evaluation Program.

Phase 2 clinical trials have as their objectives the characterization of the antitumor activity of new anticancer agents. For this reason, phase 2 trials often include a patient population different from that used for phase 1 trials, involve different endpoints, and require different levels of concomitant laboratory support.

The number of promising new agents with novel mechanisms of action has increased in recent years, and many of these new agents can only be accurately evaluated in patients in whom the cancer cells have been biologically characterized. These facts make it desirable to expand NCI support for clinical trials to establish the anticancer efficacy of these agents in parallel with appropriate biological studies of the cellular target of the particular agent. The need for increased clinical trial resources with which to perform initial phase 2 studies of this wide range of novel anticancer agents has led to this request for cooperative agreements to establish the clinical efficacy of these anticancer agents. Institutions responding to this proposed RFA should be able to perform phase 2 trials in parallel with pharmacological, immunological, biochemical, or other appropriate biological studies of the cancer cells from individual patients. The agents to be studied in these trials will be those that are of mutual interest to the investigators and NCI.

NCI will invite applications from institutions interested in performing phase 2 trials of promising anticancer agents and in conducting laboratory studies relevant to the clinical development of the agents. Scientific approaches should reflect the creativity and capabilities of investigators' studies.

Institutions submitting applications must have the following capabilities: 1) documented numbers of eligible patients with a history of adequate accrual to perform phase 2 trials; 2) laboratory support within the institution to perform pharmacokinetic studies of cytotoxic, immune modulating, differentiation inducing and/or targeted anticancer agents, including monitoring of metabolites and intracellular products when appropriate, or other relevant pharmacology correlative studies; 3) technical expertise and evidence of specific focus within the institution which would allow the measurement of response, particularly when this information would be relevant to the interpretation of the success or failure of the agent in individual patients entered into the phase 2 trial; 4) adequate central data collection and processing capabilities as well as biostatistical expertise; and 5) adequate pathology support for tumor classification and for banking and distribution of tumor tissues for concurrent and future studies.

It is anticipated that six to eight institutions will be supported on this RFA which will provide the capability of performing a total of 10 to 14 phase 2 trials annually.

Board member Donald Kufe said of the first concept, "I don't see this decreasing the efforts of phase 1 contractors. First, there are a significant number of patients at centers other than those funded

by contracts. Second, there are tremendous resources not being tapped." He questioned, however, "who is going to get" a cooperative agreement.

"It is decided by who offers to provide the greatest amount of science for the least amount of money," Friedman said.

Friedman and DCT Director Bruce Chabner discussed whether investigators on the cooperative agreements or NCI will provide the compounds. "The vast majority of compounds will be ones for which we hold the IND," Friedman said.

"It's not restricted to NCI compounds?" Chabner asked.

"It's largely restricted to that," Friedman said.

"I hope it isn't," Chabner said. "I can't imagine funding a grant and denying [a grantee] the compound."

Friedman said CTEP policy is to supply grantees the compound "if we have it." CTEP reviews their protocols "only for safety," he said.

Board members Ralph Weichselbaum (Univ. of Chicago Medical Center) and Paul Carbone (Univ. of Wisconsin), whose institutions hold some of the contracts, questioned the merits of testing compounds via grants.

"I have the highest regard for the contract holders," Friedman said. Contract holders are not restricted from applying for a grant. On the new grants, he said, NCI would try to match a compound with the skills of the institution. "The criticism I hear is that this is a closed, old boy network, so this is a way of trying to support the current excellent people in the program while bringing in new people," Friedman said.

"Where is the prioritization?" Weichselbaum asked. Friedman listed the types of compounds that NCI would like studied, such as MDR reversives, three topo 1 agents, antimetastatic agents, temozolomide, and others. "The grantee will say, 'I'd like to study X.' We will work with that individual," Friedman said. Grantees will outline general areas they want to study, and make specific proposals.

"Contractors feel somewhat put upon by this," Carbone said. He asked whether the same standards for quality assurance and protocol review would apply to the grants as to the contracts. Friedman said they would.

Carbone also noted that the phase 1 and 2 contracts were cut 15 percent a few years ago. Friedman replied, "I have continued to ask for restitution of those contract dollars." The new grants program is an attempt "to supplement [the contracts] with the only pool of money that is growing [the research project grant pool]."

Chabner concluded: "The ideas have to come from the investigators, including their own source of compound, but most of the time it will be something we get."

Both concepts were unanimously approved.

▪ ▪ ▪

Following are other concepts approved by the board at its recent meeting:

[Reports on concept reviews by the boards of scientific counselors of NCI divisions provide readers with advance notice of the Institute's spending plans. Notices of Requests for Proposals, Requests for Applications, or Program Announcements are published in ***The Cancer Letter*** *as they are released; proposals need not be submitted until that time.]*

Therapeutic studies of primary central nervous system malignancies in adults. Proposed RFA, cooperative agreements, $1.5 million per year, four years (total $6 million). Cancer Therapy Evaluation Program and Radiation Research Program.

CTEP and RRP are proposing to stimulate clinical research in the treatment of primary CNS malignancies in adult patients through the formation of a consortium of multiple institutions to perform phase I and II clinical evaluations of promising new chemotherapeutic or biologic agents and to conduct ancillary laboratory studies relevant to the clinical development of the therapeutic agents. Integrated packages of individual applications are encouraged. The lead institution of a proposed consortium will indicate which participating institutions will provide organizational support, scientific leadership, laboratory capabilities, and/or patient resources. Participating institutions will be evaluated by peer reviewers with regard to their proposed roles in the consortium, and those deemed meritorious will receive individual cooperative agreements.

A proposed consortium must have the following capabilities: (1) documented numbers of patients with CNS tumors and history of accrual of patients to clinical trials adequate for a minimum of six phase II trials (200 patients) per year, (2) laboratory support within the consortium to perform pharmacokinetic studies of both chemotherapeutic and biologic agents, including monitoring of metabolites and intracellular products when appropriate, or other relevant laboratory correlative studies; (3) laboratory support within the consortium to measure relevant indicators of biologic response; (4) adequate radiotherapy support for clinical trial utilizing radiation in combination with other modalities; (5) adequate central data collection and processing capabilities as well as biostatistical expertise; and (6) adequate pathology support for tumor classification and for banking and distribution of tumor tissues for concurrent and future laboratory studies.

It is anticipated that one consortium consisting of at least five institutions will be supported. The consortium will consist of talented and experienced individuals in multiple disciplines (e.g., medical oncology, neurosurgery, neurology, radiotherapy, molecular biology, pathology, biostatistics). Clinical trials will take advantage of new developments in drug and radiation resistance, radiation sensitizers, biological response modifiers, chemotherapy agents, differentiation agents, gene therapy, therapeutic irradiation techniques, molecular biology, or other innovative approaches. The consortium will be formed for the purpose of: (1) sharing expertise of researchers in multiple disciplines; (2) conducting joint phase I and II clinical trials to provide adequate patient populations and timely completion; and (3) sharing of tumor

specimens to conduct clinical correlative studies.

Team participants will be funded via individual cooperative agreements (U01). Participation by NCI through the program director will provide assistance in the nature of information on institute priorities and ongoing efforts elsewhere within the scientific community, as well as oversight, through the protocol review process, of methodology, feasibility, patient safety, and adherence to regulatory requirements.

Clinical trials monitoring service. Proposed recompetition of a contract held by Theradex Systems Inc., $1.583 million per year, five years. Cancer Therapy Evaluation Program.

The Clinical Trials Monitoring Service has four functions: (1) to serve as a central data management resource for phase I and certain phase II studies; (2) to conduct periodic onsite audits of selected studies as required by Food and Drug Administration regulations; (3) to co-site visit 10-20 percent of cooperative group audits of their members and/or affiliates to assure compliance with NCI, NIH, and FDA policies and regulations; and (4) to participate in on-site auditing of all other investigators/institutions conducting trials with the Div. of Cancer Treatment sponsored investigational agents at least once every 3 years.

Future plans and objectives: (1) Data monitoring of phase I and selected phase II trials of cytotoxic drugs and biologic agents, (2) on-site auditing of the same studies, and (3) assisting DCT in site visit monitoring of cooperative groups and other investigators/institutions engaged in DCT-sponsored investigational drug studies. A central database of patient information for phase I cytotoxic and biologic agents studies is maintained. At least 80 percent of the data submissions are now on tape or via computer. These same studies will be monitored through data audits conducted three times each year; audits for phase II-III contractors will be done annually. Co-site visiting about 10-20 percent of cooperative group institutions (on average, 25/year) will continue. Planning, organizing, and conducting site visits to cancer centers and other institutions will proceed.

Synthesis of chemical modifiers of radiation response. Proposed recompetition of a contract held by Auckland UniServices Limited, $650,000 per year, four years (total $2.6 million). Radiation Research Program.

The purpose of this research contract is to synthesize, characterize, and perform preliminary in vitro and in vivo testing of new compounds that modify the effects of ionizing radiation. Four major classes of compounds have been identified as the most promising and most appropriate for development under a synthesis contract:

--Bioreductive agents: bioreductive agents are metabolically reduced in hypoxic cells to highly cytotoxic products. SR 4233 (NSC #130181) is an example of such a compound. It was synthesized under an earlier radiosensitizer synthesis contract by SRI International, and is currently in clinical trials. Further exploration of this class of compounds is needed.

--Modifiers that exploit tumor pathophysiology: Transient changes in capillary blood flow may result in acute hypoxia in subpopulations of tumor cells. Chronically hypoxic cells may occur as a result of tumor pressure or the limited diffusion distance of oxygen. There may also be low extracellular pH in such regions. Therapeutic approaches for overcoming such conditions offer a possibility for therapeutic gain (i.e., greater enhancement of tumor response than of normal tissue response).

--Inhibitors of repair of radiation damage: Most radiotherapy is administered as a series of treatments over a period of several weeks, or continuously over several days. This allows for considerable repair of radiation damage in both tumor and normal cells during the course of treatment. Tumors that are highly capable of repairing radiation damage, as indicated by a cell-survival curve with a large shoulder, are particularly resistant to radiotherapy. Inhibitors of repair of radiation damage would be appropriate for such tumors. This class of radiation modifiers has not been extensively explored.

--Free-radical-based therapies: Agents that mimic superoxide dismutase and prevent damage from superoxide, hydrogen peroxide, and hydroxyl radicals produced by radiation are of considerable interest. The nitroxide Tempol is an example of this class. It protects aerobic cells and sensitizes hypoxic cells to an extent that they do not differ in their radiosensitivity.

Cooperative agreements for trials on biological response modifiers. Proposed special action, 10 awards, $200,000 per award per year ($2 million total per year), four years. Biological Response Modifiers Program.

Board approval is requested for the following:

--To increase the funding limit approved by the board for the previous RFA, allowing up to five more awards. The total number of awards would then be no more than 10 at $200,000/award/year.

--To endorse a request to the National Cancer Advisory Board (NCAB) for a mail ballot, if needed to allow award of this year's initiatives by Sept. 30, the end of the fiscal year.

--To re-issue the Cooperative Agreements for Trials on Biological Response Modifiers (CATBRM) RFA for a second year. The proposed first year award for this initiative would be 10 awards at $200,000/year/award for a total of $2 million/year.

At its February meeting, the Board of Scientific Counselors approved the concept of issuing an RFA to establish cooperative agreements for novel clinical trials of biological response modifiers. An amount of $1 million was approved in year one, for up to five awards. Response has been excellent--37 applications were received, many from highly experienced investigators. Review by an ad hoc study section was scheduled for May 31-June 3, with NCAB review in September. Because of the timing of the review relative to scheduled NCAB meetings, it may be necessary to request a mail ballot of NCAB for funding of these grants before end of the fiscal year.

In order to continue and extend funding for this highly promising area, the Biological Response Modifiers Program requests BSC approval to re-issue this initiative in FY 1993.

It is proposed that cooperative agreements be established to fund CATBRMs for the design and execution of novel clinical trials of BRMs. Applicants will be expected to propose a novel plan for early clinical development that is adequately supported by their own prior preclinical and, if appropriate, clinical results. The proposal should include evidence of access to the agents proposed for study, preclinical evaluation indicating that an investigational new drug filing is appropriate, and a detailed plan for a pilot clinical trial. NCI will facilitate the institution of a peer-reviewed, investigator-initiated trial, providing as needed (1) NCI contractor-supported production of agents; (2) where desirable, NCI holding of the IND (in which case Cancer Therapy Evaluation Program approval of the clinical protocol will be required); (3) assistance with toxicology testing, if necessary and appropriate, through a preclinical coordinator from the Developmental Therapeutics Program; (4) assistance with planning and support of a wider range of subsequent clinical trials, if appropriate; and (5) regulatory and technical expertise. Commitment of substantial NCI resources would also require Decision Network Committee approval of the agent(s) being tested.

Each group will be composed of the following elements: a principal investigator, one or more laboratory programs with the

demonstrated expertise to design and carry out assays for the appropriate monitoring of patients on the study, one or more clinical programs each headed by a program leader with demonstrated expertise in conducting clinical trials of BRMs, and an NCI coordinator. The principal investigator will be the conceptual focus of the group. The proposal may include collaborators from the principal investigator's institution, other institutions, or industry. The structure of these CATBRM groups will thus parallel that of the National Cooperative Drug Discovery Group (NCDDG) and the National Cooperative Anticancer Model Development Groups. Participation in CATBRMs will include academic, nonprofit, and/or commercial institutions. The current number of applications suggests that this approach may improve access to a wider range of creative talent.

News Roundup

Taxotere Encouraging In Early Trials; NCI, Yakult In Agreement For CPT-11

Results of **phase 1 trials of taxotere** in Europe and the U.S. "give hope that taxotere will be equally as active as taxol in ovarian cancer and breast cancer," according to NCI Div. of Cancer Treatment Director Bruce Chabner.

Data from the trials were presented at the American Society of Clinical Oncology annual meeting in San Diego in May, and at the NCI-EORTC meeting in Amsterdam earlier this year.

"The numbers of patients treated are quite small, but responses have been observed in each of these diseases," Chabner said to the DCT Board of Scientific Counselors at its recent meeting. "While taxotere evaluation is somewhat behind that of taxol, this drug, if active, should have a positive role to play in the U.S. for at least two reasons: it is produced by semisynthesis from a plentiful precursor found in Taxus leaves, and thus could provide a readily available alternative to taxol; and secondly, it provides the best guarantee for fair pricing of taxol, namely competition."

In May, NCI signed a Cooperative Research & Development Agreement with the maker of taxotere, Rhone-Poulenc Rorer, to conduct certain clinical trials of the drug.

• • •

Camptothecin analogs: NCI also has signed an agreement with Yakult to begin trials of CPT-11, a camptothecin analog with activity in colon and ovarian cancer, lymphomas and non-small cell lung cancer. More data is available on CPT-11, developed in Japan, than the NCI/Smith-Kline drug topotecan, Chabner said. A third derivative, 9-amino-camptothecin, will enter trials "in the near future," he said.

"We are particularly interested in CPT-11 because of its potential for combination with 5-FU in colon cancer and cisplatin and VP-16 in lung cancer, and intend to pursue these objectives through the cooperative groups in the coming year," Chabner told the BSC.

Chabner compiled an overview of the response rates for various types of cancer to CPT-11 from studies presented at ASCO this year:

Non-small cell lung cancer: 57%, abstract no. 978. Cervical cancer: 24%, abstract no. 708. Lymphomas (NHL): 48%, abstract no. 1070.

Following are response rates in studies presented at ASCO in 1991: Ovarian cancer: 21%, abstract no. 617. Colon cancer: 46%, abstract no. 408.

"There is justification for enthusiasm about this unique class of compounds," Chabner said.

"The most significant new agent discussed" at both the ASCO and Amsterdam meetings was temozolomide, a close structural analog of DTIC, Chabner said. "It undergoes spontaneous activation to the intermediate, methyl-triazino-imidazole carboxamide, and in early trials has shown very startling response rates of greater than 50 percent in phase 1-2 trials in primary brain tumors," he said. Responses in six of 12 patients were documented by improvements in CAT scans and in patients' symptoms. Toxicity was mild to moderate neutropenia.

Developmental Therapeutics Program Director Michael Grever negotiated with representatives of the Cancer Research Campaign in England to secure an agreement for joint development of this drug in the U.S. NCI's Cancer Therapy Evaluation Program has bulk material on hand and clinical trials could begin before the end of the year.

• • •

A personal statement: "I would like to offer the opinion that the ASCO/AACR meetings were the best I have attended," Chabner said to the BSC. "Significant new work was presented in the area of drug resistance, including studies of non-pgp-mediated MDR, guanine methyl transferase, DT diaphorase, and a host of interesting new drugs" particularly the enediynes from the Scripps Institute.

However, Chabner said, "It is ironic that in the midst of the most exciting era for cancer biology and medical science in general, and the increasingly successful application of basic work to diagnosis, treatment and prevention, both basic and applied cancer research should come under scathing attack.

"Dr. Samuel Epstein, a professor of environmental and occupational health science at Univ. of Illinois, has led an attack on NCI in the lay press, an in a presentation before the NCAB (**The Cancer Letter,** May 15). Dr. Epstein and his supporters, who

primarily work in the field of occupational diseases, decry NCI's research agenda and NCI's 'denigration' of occupational causes of cancer. I believe that NCI staff effectively refuted much of his argument. NCI spends at least 15 percent of its budget on environmental carcinogenesis and other aspects of primary prevention, although there is some disagreement between Epstein and NCI staff on these definitions. The actual estimates of the importance of environmental carcinogenesis differed greatly, Dr. Epstein quoting a figure of up to 20 percent from older studies, while NCI staff offer estimates of 4 percent or less. Clearly, Dr. Epstein believes NCI and the cancer establishment pay too much attention to basic research and treatment and too little to occupational exposures. Fortunately, it did not seem that his 'facts' or his arguments won support from the NCAB.

"For most oncologists and patients, progress in therapy has indeed been too slow, but I am convinced that the knowledge gained in the past 30 years, both in basic and applied cancer research, has benefited thousands of patients and has been more than worth the investment," Chabner continued. "The quickening pace of drug discovery and the applications of molecular biology and immunology to diagnosis and treatment give us further cause for hope for the future.

"I am further convinced that no matter how successful we will be in identifying factors that cause cancer, the issue of improving patient management cannot be relegated to a secondary status. It is unlikely that this disease, or group of diseases, will be eradicated in a single preventive stroke in our lifetime. The cause of cancer are multifactorial, a complex interplay of genetic susceptibilities, diet, environmental and even occupational exposures. Can we reasonably expect that the identification of any one or several factors will allow eradication of the disease? Even when we can implicate a proximate cause, such as tobacco, successful prevention eludes us. It is likely that the disease will persist as a problem of our aging population for years to come, and, unless we are immune to human suffering, better treatment must remain a high priority."

NCI Officially Announces Termination Of Outstanding Investigator Grants

Following is NCI's announcement of the procedures it will follow for termination and phase out of the Outstanding Investigator Grant:

NCI, with the concurrence of the National Cancer Advisory Board, announces plans for the orderly phase out and termination of its Outstanding Investigator Grant (OIG) program (**The Cancer Letter,** June 12). All non-competing commitments for future year support made to current grantees will continue to be honored as indicated on the current Notice of Award.

This announcement makes permanent the moratorium on new (Type 1) applications announced previously (**The Cancer Letter,** May 1). Any Type 1 OIG awards made in fiscal 1993, based on previously reviewed applications, will be for a 7-year project period and will be non-renewable as an OIG as a condition of award.

Currently funded OIG investigators who already have submitted either original or amended competing continuation applications (Type 2) for the June 1, 1992 receipt date for consideration at the January 1993 National Cancer Advisory Board meeting will be considered to have submitted a final competing application. Competitive but unfunded Type 2 applications from that Board round will be kept in an eligible status for an additional fiscal year. Therefore, such applicants will not be permitted to submit an amended competing continuation application for the subsequent receipt date. Where necessary to allow an orderly transition to other support, OIG grantees may request administrative extensions without additional funds for up to one year.

For all other current OIG awardees, a final round of Type 2 competing continuation applications will be accepted for the June 1, 1993 receipt date under the conditions specified below. This will be the last competing receipt date for the program prior to its termination.

1. Only investigators whose current OIG awards will be in the -05 or -06 year in fiscal 1993, and who have not submitted a competing application for the June 1992 receipt date, may submit a final, non-renewable competing continuation application on June 1, 1993, requesting up to seven years of additional support starting on the next closest anniversary date of the current award. The first competing year proposed budget may not be increased more than 15 percent over the last non-competing (-07) year actual award. Applications requesting a budgetary increase of greater than 15 percent above the -07 year level will be accepted only with the prior approval of the NCI Executive Committee. Periods of time less than seven years may be requested for this class of application.

2. Any other investigator holding a non-competing Type 5 NCI OIG award may, regardless of current non-competing years remaining, at his/her own option, submit for the June 1, 1993 receipt date a final, non-renewable competing continuation application requesting five additional years of support, with the new budget period to commence from the next closest immediate anniversary date of the current grant period following selection for funding. This submission will not place at risk the current award, should the competing continuation application fail to be funded. The first competing year budget may not request more than a 10 percent increment over the comparable recommended budget level in the current award. Future year requests may not exceed current NIH award increment policies.

Although funds for these awards are provided for in the projected plans of the NCI, given the uncertainties of budgets for future fiscal years, it would be prudent for all applicants to submit individual research project grant applications (R01 or P01) at the appropriate time as alternative potential means of support should the competing continuation OIG application not be funded.

Current OIG awardees are strongly encouraged to contact the NCI program official identified on the Notice of Award to discuss future options for the transition from support under the OIG to support under other investigator-initiated grant mechanisms.

For additional information or for questions concerning this notice, contact: Barbara Bynum, Director, Div. of Extramural Activities, NCI, Bldg. 31 Rm 10A03, Bethesda, MD 20892; phone 301/496-5147, fax 301/402-0062.