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Clinical Study Section's Workload Up 50 Percent, Evidence That More Investigators Submitting R01s

It is the first indication that clinical investigators are heeding the call of NCI Director Samuel Broder to seek funding through the traditional NIH research project grant mechanism: 50 percent more clinical cancer related R01 applications currently are being reviewed by the Experimental Therapeutics 2 study section than were reviewed in the first part of last year. However, the actual number of applications is still

(Continued to page 2)

In Brief

David Feigal To Head FDA's Antiviral Division; ODAC To Discuss Melphalan, Amifostine NDAs

DAVID FEIGAL has been named director of FDA's Div. of Antiviral Drug Products, the division that has primary responsibility for evaluating antiviral and anti-infective AIDS treatments. **Carl Peck**, director of FDA's Center for Drug Evaluation and Research, served as the division's director since January 1991 after the departure of **Ellen Cooper**, the division's first director. Feigal was associate professor at Univ. of California (San Diego) Medical Center. He played an instrumental role in several major clinical trials, including those for experimental AIDS therapies. In 1989, he was appointed to a four-year term as a member of FDA's Antiviral Drugs Advisory Committee. . . . **FDA's ONCOLOGIC DRUGS** Advisory Committee will meet Jan. 31, 8 a.m., Conf. Rms. D & E, Parklawn Bldg., Rockville, MD, to discuss new drug applications for Alkeran (melphalan) for injection, Burroughs Wellcome, for hyperthermic isolated limb perfusion as an adjunct to surgery for locally advanced malignant melanoma of the extremity and for palliative treatment of multiple myeloma; and Ethyol (amifostine) injection, U.S. Bioscience, as a chemoprotective agent against the serious toxicities associated with intensive regimens of platinum and alkylating agent chemotherapy. Contact Adele Seifried, 301/443-4695. . . . **VINCENT DEVITA**, Memorial Sloan-Kettering Cancer Center and former NCI director, has been elected to the board of directors of **ImClone Systems Inc.** The company is developing therapeutic products to treat selected cancers. Phase 1 trials recently began of its BEC-2 therapeutic for malignant melanoma. . . . **TAMOXIFEN TRIAL** for breast cancer prevention in 16,000 women will begin in March, sources say. The National Surgical Adjuvant Breast & Bowel Project, which is coordinating the trial, has selected the sites and met with site representatives. The trial's opening will be officially announced at a Washington press conference.

ET2 Workload Up 50 Percent Thanks To Clinical Investigators

(Continued from page 1)

relatively small: 13 applications reviewed in round 1 versus 26 applications submitted for round 2, according to staff in NCI's Cancer Therapy Evaluation Program who are following the statistics with great interest. Those represent only applications submitted in response to CTEP iniatives.

Still, it is early in the game. Broder and key members of his staff began talking about increasing the number of clinical R01 grants last year, NCI advisors approved several new initiatives to encourage applications, and clinical investigators are just now submitting their proposals. How the round 2 investigators will fare in ET2 will not be known for about another month.

NCI executives have been encouraged by the preliminary results.

"We don't know if this is a continuing trend or a one-time burst, but it is a significant increase," CTEP Director Michael Friedman said recently of the ET2 workload.

The next round of grant review takes place in March, and results are submitted for approval at the May National Cancer Advisory Board meeting.

"This is just when we'd see some activity," Marvin Kalt, deputy director of the Div. of Extramural Activities, told **The Cancer Letter** this week. "Given the length of time it takes for review, it is really over the next two cycles where we would be in a position to judge whether it's working. We are starting from a small base, so the absolute numbers are relatively small."

In addition, several new initiatives are just now or in the next several weeks will be officially announced. Two program announcements were released this week: interactive research project grants for cancer and studies on breast, prostate, ovarian and cervical cancer (see Program Announcements section of this issue).

Broder has called the IRPG initiative an "administrative experiment." The IRPG allows three or more investigators to submit collaborative R01 grants to be funded as a package.

NCI's clinical cooperative groups have been encouraged to ask their investigators to submit applications for IRPGs. With NCI's FY92 budget increase, research project grants will be funded at around the 30th percentile, in contrast to last year's 20th percentile, CTEP staff member Roy Wu noted at a recent meeting of the cooperative group chairmen.

"Cooperative groups should take advantage of this opportunity and submit R01 grants," Wu said. "I can envision a situation in which you propose a clinical trial, each lab would have an ancillary study, and each would be reviewed in a package, and you would get funding for all your studies."

Douglass Tormey, chairman of the Eastern Cooperative Oncology Group, agreed. "Our group will be forced to increase the number of grant officers. It is costly to us, and this cost is not reimbursed. However, the IRPG is exciting and investigators like it because it gives them the opportunity to work with others."

The Div. of Cancer Treatment has issued several RFAs which will use the U01 mechanism, which provides for larger scale studies. These are likely to be more relevant to cooperative groups, Friedman said.

'Send In Your R01s'

Broder and other NCI staff also have been talking directly to the ET2 study section about the effort to increase clinical R01s.

"One reason we've made so much progress in basic science is that investigators have a reasonable opportunity on their own to submit applications, and an opportunity for training and career development," Broder told the DCT Board of Scientific Counselors at its recent meeting.

"I don't think a comparable opportunity exists for those going into clinical research. I don't think we can accomplish this goal only by setting aside money for RFAs. We need to make more effective and efficient use of the RPG mechanism.

"Send in your own R01s, or encourage your colleagues to send in R01s," Broder said. "We do not want to have only a central government authority directing clinical research."

He noted that CTEP will help investigators file Investigational New Drug applications with the FDA.

DCT Board member Paul Carbone noted that "there

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was an enormous rush of RFAs this fall. There were many we could have responded to."

"Too many opportunities?" Broder asked.

"Too short deadlines," Carbone replied.

Another NCI-sponsored opportunity has a key deadline this week. Applications are due Jan. 17 for the Specialized Programs of Research Excellence in breast, prostate, and lung cancer.

Broder said the SPOREs eventually should act as "magnets" for increasing R01s in those three cancers.

At least 24 applications are expected for the prostate cancer SPORE, 22 are expected for the breast cancer SPORE, and 11 are expected for the lung cancer SPORE, according to Andrew Chiarodo, chief of the Organ Systems Coordinating Branch in the Div. of Cancer Biology, Diagnosis & Centers. Awards will be made Sept. 30.

"Young clinical investigators have come to me and said there's no way I can get funded. They're right," Broder told the DCT Board. "Clinical oncology will not have standing in an academic institution if it can't bring in grants."

DCT Board Chairman Ron Levy told Broder, "The monkey is back on our backs where you effectively placed it."

Following are Requests for Applications issued by DCT last year for which data are available on number of applications:

--DCT small grants to stimulate correlative laboratory studies and innovative clinical trials (CA-90-03). NCI received 162 applications for these R03 awards, approved 126 and awarded 23, for a total of $1.48 million. Eleven of these awardees are associated with a cooperative group. Another two awards were funded by the Wendy Will Case Foundation.

--AIDS-lymphoma network (CA-91-01): 28 applications were received, 27 were approved, and nine awards were made in FY91. Three of the awardees are associated with a cooperative group--Murphy with Pediatric Oncology Group; Gordon with Eastern Cooperative Oncology Group; and Feigal with Cancer and Leukemia Group B. A total of $3 million was awarded by NCI.

--Clinical treatment and correlates of upper GI carcinoma (CA-91-03): 22 applications were reviewed, and seven awards were made in FY91. One awardee is associated with a cooperative group. A total of $1,367,777 was awarded.

--New therapeutic approaches to the treatment of prostate cancer (CA-91-16): 18 applications received, no awards have been made yet.

DCT issued the following RFAs this fall for which no data is available yet since awards have not been made:

--Phase 1 trials of new cytotoxic and biologic agents in children with cancer (CA-91-22, **The Cancer Letter,** Aug. 23); $750,000 per year set aside, four years, U01 mechanism. Applications were due last November.

--Clinical trials of cancer therapy with biological response modifiers (CA-92-01, **The Cancer Letter,** Nov. 8), $1 million per year set aside, four years, U01s. Applications due Jan. 22. The purpose of this project is to provide funding for the development of novel approaches to the treatment of cancer with BRMs, employing new agents, concepts and treatment strategies; perform phase 1A, 1B or phase 2 clinical trials; and perform relevant laboratory studies related to clinical trials.

Several program announcements issued by DCT are still active, with applications due Feb. 1, June 1 and Oct. 1. They are followed by the dates of their publication in **The Cancer Letter:**

--Surgical oncology (PA-91-16, **CL** Feb. 1), 12 applications received.

--Clinical cancer therapy research (PA-91-42, **CL** April 19), 25 applications received, one involving Eastern Cooperative Oncology Group studies received an excellent review.

--Cancer therapy research in lung cancer (PA-91-83, **CL** Aug. 16), applications still being submitted.

--Small grants for lung, breast & ovarian cancer clinical trials (PA-92-06, **CL** Nov. 15), applications due Jan. 23.

The following concepts were approved for program announcements last fall by the DCT Board (**CL** Nov. 8 and 15); they should be issued soon:

--Biologic and therapeutic insights into the management of AIDS-Kaposi sarcoma patients.

--Novel nonionizing radiation technologies for breast cancer imaging.

The following concepts were approved for RFAs:

--Clinical correlative studies in solid tumors. U01 mechanism, $2 million per year set aside, four years.

--Clinical correlative studies in hematologic malignancies. U01 mechanism, $2 million per year set aside, four years.

Radiation Research Program issued the following initiatives:

--3-D conformal therapy: phase 2/3 prostate trials. R01s, $750,000 set aside per year.

--Quantification of tumor response to treatment: A 3-D approach. R01s, $500,000 per year set aside.

--Gene regulation of radiation resistance. R01s, $1 million per year set aside (**CL** Dec. 6).

--RDOG 4: Pediatric solid tumors and ovarian

cancer. U01s, $800,000 per year.

--Digital imaging developing group for mammography. U01s, $1 million per year.

--Tissue imaging: in vivo microscopy. U01s, $800,000 per year.

In addition, the National Institute of Neurological Disorders & Stroke issued an RFA for feasibility grants (P20s) for brain tumor research centers, with a set aside of $2 million per year for approximately eight three-year awards (**The Cancer Letter,** Oct. 11). Application receipt date was Jan. 15. Approximately 60 letters of intent were received, according to the NINDS Div. of Stroke and Trauma.

NCI's Div. of Cancer Prevention & Control also is encouraging investigator initiated applications, director Peter Greenwald said. The division's Board of Scientific Counselors this week will be asked to approve an "omnibus" program announcement seeking applications in all areas of cancer prevention and control research.

Unlike therapeutic trials, the prevention and control applications go to a wide range of study sections, Greenwald said. Over the past eight to 10 years, prevention and control research as a discipline has been expanding. Very little clinical prevention research was conducted a decade ago, Greenwald said.

"We do want to encourage investigators to come in. The historical trend has been most favorable to the R01 pool."

Greenwald said DCPC will receive a $21 million increase in the FY92 budget. "We want to put more emphasis on prevention trials, and do it largely though the CCOP program," he said. The division's Board of Scientific Counselors this week will consider whether to recommend a trial testing the drug proscar in men with A1 prostate cancer, the most localized form.

AZT, DDC Combination Increases CD4 Counts In Advanced AIDS

A recent trial sponsored by the National Institute of Allergy and Infectious Diseases indicates that combination antiviral therapy with zidovudine (AZT) and the experimental antiretroviral ddC is well-tolerated and can produce increases the CD4-positive T-cell counts in patients with advanced HIV disease.

Results of the trial, which involved 56 patients at two sites of NIAID's AIDS Clinical Trials Group (ACTG), were reported in the Jan. 1 edition of "The Annals of Internal Medicine."

However, in an editorial accompanying the report, NIAID Director Anthony Fauci noted that trial, labelled ACTG 106, "is a pilot study that awaits confirmation in a larger group of patients. The data presented are too preliminary to make a final conclusion about the toxicities of the two drugs, or to recommend treatment using a combination of ddC and AZT."

Based on the data from this study, a much larger ACTG trial, ACTG 155, involving more than 1,000 patients is now underway to compare the combination regimen to monotherapy with either drug.

"Data from ACTG 155 should provide a clear answer to the question of whether an AZT/ddC combination is superior to single drug therapy," said Daniel Hoth, director of NIAID's Div. of AIDS.

ACTG investigators at the Univ. of Miami and the Univ. of California, San Diego enrolled the 56 patients with AIDS or advanced AIDS-related complex and CD4 cell counts below 200 cells/mm^3 in the pilot study between July, 1989 and May, 1990. None of the patients had previously been treated with an antiretroviral agent; all received aerosolized pentamidine for the prevention of Pneumocystis carinii pneumonia during the study.

The patients were divided into six groups: one received the low daily dose of AZT (150 milligrams); the other five groups received various dosages of AZT (150 to 600 mg per day) and one of two doses of ddC (0.015 mg or 0.030 mg per kilogram of body weight per day).

Although patients' mean number of CD4 cells increased with all regimens, the investigators found that certain combinations of AZT and ddC increased CD4 counts to higher levels for a longer period of time than had previously been shown when persons with advanced HIV disease took either drug alone.

In addition, patients' levels of p24 antigen, a protein produced by HIV, decreased with five of the six regimens by the second week of the study, and this decrease persisted throughout the study. With the lowest dose combination regimen, the suppression of p24 levels did not occur until the eighth week of treatment.

In test tube studies, AZT and ddC together have been shown to complement each other's antiviral activity. Investigator Margaret Fischl, from the Univ. of Miami School of Medicine, said that in the current study, "the apparent increased benefit with combination therapy may be related to the additive or synergistic activity of the two drugs that has been seen previously in vitro. Also, the emergence of drug-resistant strains of HIV may have been diminished by the use of AZT and ddC together."

In addition, because the two drugs, both nucleoside analogs, have different side effects, researchers speculate that the two together might be more

effective and less toxic than either alone. The most common side effect of ddC is sensory peripheral neuropathy; AZT can cause severe anemia and bone marrow suppression.

In the study, 14 patients had 16 episodes of serious adverse events that may have been attributable to the study medications. The investigators did not find any differences in the frequency of adverse events among the various regimens studied.

Although ACTG 106 was not specifically designed to determine the optimal dose of AZT, the researchers also found that the low, 150-mg dose was less effective than the currently recommended daily dose of 500 to 600 mg.

"This observation suggests that doctors should not use the lower dose of AZT either alone or in combination with other agents, except in cases of AZT-related toxicity," said Fauci. "The currently recommended dose...remains the first-line antiretroviral therapy for patients with advanced HIV disease."

News Roundup

Former NCI Lab Deputy Charged With Two Criminal Counts

The former deputy director of NCI's Laboratory of Tumor Cell Biology has been charged with two criminal counts by the U.S. Attorney for the District of Maryland.

Prem Sarin, who was deputy to LTCB Chief Robert Gallo until his suspension last January, was charged last month with unlawfully accepting funds from a research firm as payment for "conducting and causing to be conducted virological testing research," the district attorney's office said in a press release.

Sarin was also charged with making false statements about the funds on a government financial disclosure statement.

The district attorney charged that Sarin received $25,000 from Homburg Degussa Pharma as payment for agreeing to perform virological testing in the NCI laboratory, and then falsely stated that he had agreed to "consult and lecture" at the firm for an amount not to exceed $4,500 per year. The attorney's office said Sarin was to have received another $25,000 payment from Homburg Degussa Pharma.

The charge of supplementation of income is a misdemeanor which carries a maximum penalty of one year imprisonment and $100,000 fine. The charge of false statement is a felony carrying a maximum penalty of five years imprisonment and $250,000 fine.

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Sen. Ernest Hollings (D-SC) was honored by the National Coalition for Cancer Research recently for his work to increase funding for cancer research. The Coalition presented the senator with a public service award at a benefit last month for the new Hollings Oncology Center of the Medical Univ. of South Carolina in Charleston.

Fitzhugh Mullan, president of the National Coalition of Cancer Survivors, a member organization of NCCR, presented Hollings with a statue of Don Quixote. Mullan said the statue "symbolizes very simply the fact that you have allowed many to dream the impossible dream--to have the hope and vision to eradicate cancer."

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American Cancer Society awarded more than $42 million in grants in its second round of grant funding for 1991. The Society's Board of Directors approved 169 new grants and renewed 162 for a total of 331 grants. For the year, 12 percent of new applications and 50 percent of competing renewals were approved for funding.

The Society also approved a special institutional grant to the Harvard School of Public Health for epidemiological and laboratory investigation of nutrition and cancer, and renewed an SIG at the Univ. of Nebraska for research into cancer cause and prevention.

The Harvard SIG, under the direction of **Walter Willett**, is the second such ACS grant in the area of nutrition and cancer. Willett was awarded $1 million for five years to develop the Harvard project, which seeks to determine the relation of dietary factors to important cancers, namely colon, breast, prostate and lung.

Raymond Ruddon, director of the SIG at the Eppley Institute at Univ. of Nebraska, was awarded a $1 million renewal for five years.

In other action at the Society's recent board meeting, two scientists were awarded designation as ACS research professors. The appointments of **Edward Harlow**, Massachusetts General Hospital Cancer Center, and **Christine Guthrie**, at the Univ. of California (San Francisco), bring the number of ACS research professors to 24.

Assuming the awards remain in effect until the professors retire, the total awarded would be a little over $1 million each. The awards are subject to scientific review every five years.

The awards free the recipients from academic tasks such as teaching and administrative duties and allow them to concentrate solely upon research.

RFPs Available

Requests for proposals described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs, citing the RFP number, to the individual named, the Executive Plaza South room number shown, National Cancer Institute, Bethesda MD 20892. Proposals may be hand delivered to the Executive Plaza South Building, 6130 Executive Blvd., Rockville MD. RFP announcements from other agencies will include the complete mailing address at the end of each.

RFP NCI-CP-21006-02

Title: Operation and coordination of a nationwide, multi-study, high-volume death certificate acquisition and management system

Deadline: Approximately March 9

The Biostatistics Branch, Epidemiology & Biostatistics Program in NCI's Div. of Cancer Etiology, conducts epidemiological studies to define the distribution and determinants of cancer in man. Cohort followup and case-control study designs are commonly used. The names of study subjects are obtained from hospitals, clinics, unions, companies, professional societies, federal, state and local governments and other such organizations. Subjects include individuals who may have been at risk to cancer due to exposures such as chemicals, drugs, food components, biological agents or radiation. Exposures may have occurred 20 to 50 years ago in some studies. Many studies require locating persons to determine current vital status, i.e., dead or alive. It is crucial to locate a maximum number of study subjects and acquire the death certificates of those who died in order to examine them for a diagnosis of cancer.

An NCI project officer and multiple assistant project officers will monitor the work of this project, which is expected to last for a period of five years. Each APO is an NCI investigator who originates a particular death certificate acquisition task and monitors the work performed by the contractor.

The EBP is seeking a contractor with a primary objective to acquire large numbers of death certificates simultaneously from Vital Statistics Offices of multiple states (sites) using the contractor's own distinct automated system. This procurement is a recompetition of an ongoing contract which is being performed by Westat Inc. The existing contract expires on May 31, 1992.

An automated system is necessary because of the complexity and large volume of work involved. Emphasis will be placed on the location and description of the physical facility in which the automated system is located and a description of the system as a distinct system within the company. An average of 12,000 death certificates per year will be requested from VSOs throughout the U.S. About 1,000 death certificate requests will be sent to multiple VSOs per month and an approximately equal number of certificates will be returned from these sites monthly. The exact number and nature of studies that will require support under this procurement cannot be accurately projected at this time. It should be noted that 25 or more studies requiring nationwide data gathering and death certificate acquisition activities are ongoing in the EBP at any point in time.

The NCI project officer will provide the contractor with lists which show all pertinent information available on each deceased subject, such as date of death, town or city and/or state of death, as well as other known personal identifiers. For some decedents, requests to several states may be necessary. The contractor shall use its automated system, assigned personnel, knowledge and experience to perform all of the logistical activities and procedures in order to accomplish the necessary death certificate acquisition tasks requested. Rigorous quality control procedures must be followed at all times. Puerto Rico and other U.S. possessions may be included as necessary. Detailed information shall be kept on all outgoing and incoming materials, including logs, records and forms.

Death certificates received by the contractor shall be carefully examined and classified as Found, Not Found, or Out of Scope. Matching is based on the agreement of information on the death certificate with information and identifiers on subjects which the contractor has. Matching shall be done by experienced key personnel, as it is a very important step in the process. The contractor shall be required to submit monthly and annual technical progress reports and a final report.

The offeror should provide tabulation and description of current pertinent regulations and requirements of each VSO throughout the country for acquisition of death certificates. A description, as well as curriculum vitae, of the death certificate acquisition manager's capabilities and experience in high volume, multi-state/site/VSO death certificate acquisition, and in supervision of an automated system should be provided. The death certificate acquisition manager should have experience managing the automated system. It is estimated that the total level of effort for the five year period of performance will be 13,500 direct labor hours. All key personnel combined should equal one person year.

Contract Specialist: Michael Loewe
RCB Executive Plaza South Rm 620
301/496-8611

Program Announcements

PA-92-29

Title: **Interactive Research Project Grants for Cancer**

Application Receipt Dates: Feb. 1, June 1, Oct. 1

Complex questions in cancer research often require investigative efforts that extend beyond the level practicable in a single project or that require a mixture of technical approaches beyond the means of a single investigator. The perceived merit of individual research project (R01) applications sometimes may be limited by the lack of a comprehensive, interdisciplinary approach, or by limitations in resident technical expertise. There also may be areas of investigation that are under-represented in applications because they cannot effectively be exploited without a collaborative effort, yet local opportunities for such interactions are not available.

NCI, under an Interactive Research Project Grant announcement, seeks to encourage the coordinated submission of related research project grant applications from investigators who want to collaborate on a common cancer research theme, but do not require extensive shared physical resources or core functions. A minimum of three independent investigators with related research objectives are encouraged to submit concurrent, collaborative, cross referenced individual research project grant applications (R01) that share a common research focus. Applications may be from either a single institution or a consortium of institutions. Applications will be reviewed independently for scientific merit. Meritorious applications will be considered for funding both as independent awards and int he context of the overall proposed collaboration.

Historically, NCI has relied on multi-component awards, such as program projects (P01) and Cancer Center Support Grants (P30), to encourage interdisciplinary collaborations in areas requiring integration and central direction of basic and clinical research components. A hallmark of such awards is the provision for extensive core facilities/resources and appointment of a program director to manage the overall effort.

For many research areas it may be more appropriate to consider an intermediate level of collaboration, less extensive than that described above, but beyond that practical for single projects. For such intellectually driven collaborative efforts, the exchange of data, materials, and ideas, rather than shared physical resources or central oversight, is the primary requirement. The concept of IRPGs set forth in this announcement is meant to address and facilitate this class of research activities. Typically, the IRPG approach will be suited to many basic research questions as well as research to develop, apply and evaluate interventions for cancer prevention and control. The IRPG mechanism may also fit well with clinical applications that propose limited testable research questions or with focused phase 1 and 2 therapeutic and related correlative laboratory studies.

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 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. Each grantee will have the ability to submit on his/her own behalf competing supplements as appropriate to incorporate promising new directions of research as they evolve. The freedom to establish collaborations on an equal footing at separate sites (including foreign locations), and the improved transferability of awards made to individual principal investigators, also are significant benefits. In contrast, translational research programs that span a variety of disciplines and programs that require extensive co-located core resources, would continue to be served best by traditional multi-component program award mechanisms.

NCI encourages qualified investigators to develop and submit concurrently coordinated research project applications that address areas of relevance to cancer in which the interactive research project concept may be applied. Applications submitted as a package should be tightly focused and the interactions and benefits of the proposed linkages should be made explicit as explained below.

IRPG applications will be accepted in any relevant area of cancer research where this mechanism may be constructively applied. Some typical examples:

--Immunobiology of specific cancers, such as breast, ovarian, and prostate. Since these cancers involve both immune and neuroendocrine responses, projects requiring expertise in various aspects of cancer biology, immunology, and/or endocrinology will be needed for a comprehensive approach for these questions.

--Hormones and signalling pathways. Basic science projects may be combined that integrate multiple aspects of hormonal regulation of cancer from growth factors to receptors to signal transduction to genetic regulation.

--Detection and intervention studies in breast and other cancers. New methods are needed to promote the use of detection methodologies in populations at risk and to measure the efficacy and compliance with recommendations. Studies to identify and overcome barriers to health promotion and to measure cost-effectiveness may also be linked to such a program.

--Focused studies on phase 1 and 2 clinical trials. Projects designed to investigate promising combined therapeutic approaches to a single type of cancer may be linked with correlative laboratory investigations to investigate further the mode of action and/or biological effects of treatments.

--Related basic studies focused on multiple facets of common viral or chemical carcinogenic agents such as HIV or human papilloma virus, that do not require extensive core resources.

--Basic drug discovery programs that focus on multiple aspects of a related class of compounds or on a single mechanism of action.

--Methodologically related applications that focus on development and/or application of specific methodologies to cancer research, where extensive shared physical resources are not required.

--Research on variations in control of the cell cycle that operate specifically in tumor cells. Projects might focus on unique enzymes or effector molecules, the role of protein modifications such as phosphorylation, activation of oncogenes and interactions with suppressor genes.

Prospective applicants are encouraged to explore other areas of potential for the IRPG mechanism with NCI program directors.

Support for this program will be by the R01 grant. One principal investigator out of the group must be identified as the program coordinator and must be cited in all applications on page 2 of form PHS 398. Individual investigators may request funds for the time and effort contributed toward the coordination of the overall research and for collaborative resource activities.

Each application must be complete in itself with all appropriate approvals, budgets, and signatures.

Requests for limited shared resources must be proportionally budgeted in each application based on anticipated use, with a full explanation given in the budget. Personnel time and effort requests for management of shared resources are allowable. If consortium arrangements between independent institutions are proposed that would make transfer of funds for required new equipment impractical, the entire equipment request may be budgeted by the responsible laboratory. This should be clearly justified.

Domestic and foreign nonprofit and for profit organizations, institutions, governments and their agencies are eligible to apply.

Each application will be considered on its own merit as an individual research project. Applicants may not concurrently submit R01 applications that represent significant duplication of the efforts described in the IRPG. NCI will consider funding meritorious individual IRPG applications if it is not possible to fund the IRPG package as a whole. Concurrent submission of P01 applications that request support for essentially similar work is also prohibited.

Insofar as possible, assignment of each IRPG application will be to a standing Div. of Research Grants initial review group, that may be supplemented by consultants. Applications utilizing widely differing approaches will not necessarily be reviewed by the same initial review group.

Although there is no set aside of funds committed to the IRPG mechanism, NCI will consider for funding all IRPG applications in a cohort if all are rated by peer review as having significant and substantial scientific merit.

Written and telephone inquiries concerning the objectives and scope of this program announcement are encouraged and may be directed to: NCI Referral Officer, Review Logistics Branch, Div. of Extramural Activities, NCI, Westwood Bldg. Rm 850, Bethesda, MD 20892, phone 301/496-7173, fax 301/402-0275.

PA-92-27

Title: **Studies on breast, prostate, ovarian, and cervical cancer**

Application Receipt Dates: Feb. 1, June 1, Oct. 1

The U.S. Congress included the following language in the conference report accompanying the fiscal year 1992 appropriation bill for Labor, Health and Human Services, Education and Related Agencies: "The conferees express their serious concern about the growing epidemic of breast and prostate cancer in the U.S. The conferees urge, in the strongest way, that the National Cancer Institute make breast, prostate,

ovarian and cervical cancer its top priorities and treat these diseases with utmost urgency."

This program announcement serves to notify and reaffirm to the scientific community the continuing interest of NCI in expanding research support in basic and applied studies of the etiology, biology, diagnosis, treatment and prevention of these specific cancers as a matter of high Institute priority.

Support of this program will be by research project grants (R01), program project grants (P01), First Independent Research Support and Transition (FIRST) awards (R29), Outstanding Investigator Grants (R35), and Method to Extend Research in Time (MERIT) awards (R37). In addition, competing supplemental applications to active grants under these support mechanisms and research project cooperative agreements (U01), except for the FIRST award, are specifically encouraged to pursue new promising avenues of research.

Applications may be submitted by domestic and foreign, for profit and nonprofit organizations, units of state or local governments, and eligible agencies of the federal government.

NCI is composed of four program divisions that support extramural research relevant to this program announcement. The spectrum of research supported by these divisions is as follows:

▸Div. of Cancer Etiology plans and directs a national program of basic research including laboratory, field and epidemiologic and biometric research on the cause and natural history of cancer and means for preventing cancer, and evaluates mechanisms of cancer induction and promotion by chemicals, viruses, and environmental agents. Representative types of research activities appropriate to this program announcement include but are not limited to: assessment of the relative contributions and interactions of lifestyle, environment, occupation, genetic factors, viruses, and/or metabolism on the risk of cancers of the breast, prostate, ovaries, and cervix. In addition, integrated multidisciplinary studies in chemical carcinogenesis are encouraged to identify epithelial cell markers for various stages of transformation, to identify inhibitors of carcinogenesis including natural inhibitors in the human environment, and to determine the specific molecular changes that occur as epithelial cells are transformed. Finally, studies are specifically solicited to identify protective epitopes of the human papillomaviruses associated with cervical carcinoma, that are necessary for the preparation, testing, and eventual production of protective therapeutic vaccines for this form of cancer.

▸Div. of Cancer Biology, Diagnosis & Centers supports research on the cellular and molecular biology of malignant cells, the role of the immune system in tumor growth and progression and on the transfer of basic research findings to clinical application for the improved diagnosis/prognosis of cancer. In the area of cancer biology, areas of emphasis include, but are limited to: soluble factors (e.g., hormones, growth factors), and matrix and membrane macromolecules that modulate the growth of tumor cells; the regulation of the expression of these effectors and the mechanism of action; and the genetic events responsible for progression of tumors to a highly malignant and metastatic state. In the area of cancer immunology, specific interests include but are not limited to: cellular and humoral immune recognition of tumor antigens, methods of improving immune killing of tumor cells, immune control of tumor metastasis, other regulatory effects of the immune system on tumor growth, and tumor modulation of host immune function. Studies are specifically solicited for further research in these areas of immunology aimed at the eventual development of vaccines for the primary or secondary prevention of these cancers. In the area of cancer diagnosis, areas of emphasis include but are not limited to: more precise staging of tumors for prognostic and therapeutic decision making, more effective monitoring of response to therapy, earlier detection of both initial and recurrent tumors, and identification of populations at risk for developing particular cancers.

▸Div. of Cancer Prevention & Control plans, develops, directs and coordinates research on prevention, control, and community oncology. Representative studies involve the identification and evaluation of agents that may inhibit carcinogenesis (initiation, promotion, transformation, and/or progression). These studies could include identification of appropriate agents through literature searches or laboratory methods, efficacy and toxicology studies in animals to aid in selection of materials for human studies, and phase 1 and 2 clinical trials of potential preventive agents. Other research could focus on reduction of cancer morbidity and morality through early detection including identification of biological markers of risk, exposure, and pre-malignant events of progression. Research on the roles of nutrients, food groups, and other dietary components in cancer incidence is appropriate including the influence of dietary factors on the modulation of cancer risk markers or intermediate endpoints. Cancer control includes research on the development and testing of intervention strategies to modify personal, social, and lifestyle factors known to contribute to the development and/or increased risk of cancer, and multidisciplinary intervention research aimed at addressing minority, underserved, and other special populations. Research under this program announcement also may include data collection, statistical analysis and mathematical modeling, health services research, and information database linkage studies to monitor progress toward cancer control, particularly pertaining to the PHS "Health People 2000" National Goals.

▸Div. of Cancer Treatment plans, directs, and coordinates an integrated program of preclinical and clinical cancer treatment research with the objective of curing or controlling cancer in humans by utilizing single or combination treatment modalities. The tumors addressed by this program announcement currently require multimodality treatment for optimal management of all stages and presentations of disease, but these treatment methods cause serious morbidity and fail to cure most patients with advanced disease. In preclinical cancer treatment research, there is an urgent need to translate recent developments in the molecular biology of cancer into the discovery of new anticancer treatments whose actions will be highly specific for particular genes or gene products. Exciting areas that may be exploited include oncogenes such as the HER-2/neu oncogene in breast cancer, suppressor genes, signal transduction, cell cycle regulation, growth factors/receptors, metastasis, and angiogenesis. Several approaches will be necessary to take advantage of these new opportunities. Additional topics include, but are not limited to: drug discovery of new anticancer agents, biochemical and molecular mechanisms of antitumor drug action, and pharmacology and toxicology of antitumor agents. Studies to circumvent individual and multiple drug resistance and prevent metastasis of these cancers to other organs are included. Clinical research opportunities exist in the areas of high dose chemotherapy followed by autologous bone marrow rescue, multidrug resistance, radiosensitizers, adjuvant chemotherapy, innovative surgical or multimodality approaches, particle beam irradiation, novel immune therapies and genetic manipulations of host or malignant tissues, therapy with biological products, such as interleukins, monoclonal antibodies, and/or retinoic acid. Applications that address these opportunities and these particular tumors are specifically solicited.

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