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NCI Advisors Reject $30 Mill. Cohort Study, Approve Renewal Of Phase I Initiatives

By Kirsten Boyd Goldberg

Advisors to NCI rejected the institute's plan to renew funding for the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS), a $30-million, five-year initiative of the Division of Cancer Control and Population Sciences.

The NCI Board of Scientific Advisors at its meeting June 29-30 rejected the project on a 10-4 vote, following an unusually short discussion.

Over the past six years, the consortium collected data from 5,000 lung cancer patients and 5,000 colorectal cancer patients to study cancer care and outcomes. BSA Chairman Robert Young, president of Fox Chase

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In the Cancer Centers:

Scardino Named MSKCC Surgery Chairman; Sawyers To Lead Pathogenesis Program

PETER SCARDINO, a urologic surgeon, was named chairman of the Department of Surgery at Memorial Sloan-Kettering Cancer Center, said **Robert Wittes**, physician-in-chief at MSKCC. Scardino, who was inaugural chairman of the Department of Urology since 1999, is known for his work developing techniques to decrease the effects of surgery on urinary and sexual function and to improve the chances of long-term cancer control by the total removal of the prostate. In 2001, Scardino received a grant from NCI to create a new Specialized Program of Research Excellence in prostate cancer at MSKCC. He is head of the Prostate Cancer Program and holds the Florence and Theodore Baumritter/Enid Ancell Chair of Urologic Oncology at the Center. Scardino is professor in the Department of Urology at the Weill Medical College of Cornell University and holds the same position at the State University of New York Downstate Medical Center. He replaces **Murray Brennan**, who stepped down after more than 20 years and will continue to treat patients and conduct research at MSKCC. . . . **CHARLES SAWYERS**, physician-scientist at Memorial Sloan-Kettering Cancer Center, was appointed chairman of the new Human Oncology and Pathogenesis Program and the first incumbent of the Marie Josée and Henry R. Kravis Chair. The program will focus on cancer cell biology and molecularly targeted drugs and other interventions. HOPP will bring together physician-scientists from clinical and scientific disciplines to conduct translational research across many types of cancer. . . . **ROSWELL PARK Cancer Institute**

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CanCORS Concept "Unclear," BSA Chairman Young Says

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Cancer Center, said the project "doesn't seem to be enormously productive" since it has resulted in just seven publications, several of which are simply descriptions of the initiative.

"This [concept statement] describes to me the creation of a new cohort," Young said. "I would sure like to see what happened to the last cohort before I created another one. It also calls for the collection of tumor blocks and blood samples, and all sorts of stuff to do a biospecimen repository. Perhaps we traveled enough of that ground at this point. It's creating a scientific chair of a group, which suggests to me a sort of permanent character, and I sense a shift away from what this started out to be, which is, what happens to people when they are supposed to be treated…. Six years into this, I couldn't give you a single sentence about what that is. So I have a real serious problem knowing where this next 30 million bucks is going to go."

Program director Arnold Potosky said the eight organizations in CanCORS are writing 15 papers, and the project is still collecting medical data. The productivity is similar to other large studies involving a number of organizations, he said.

"This is an incredibly valuable program of research," said BSA member Susan Curry, director of the Institute for Health Research and Policy at the University of Chicago. "It's the only study I'm aware of where you're in front-line clinical practice, and you're able to triangulate biologic, patient data, caregiver data, physician data, to understand what's being delivered, why it's being delivered, and what the outcomes are. Launching that kind of an effort is incredibly complex…. I think it's a real data treasure."

Curry made the motion to approve the concept. Six BSA members abstained from voting.

Following the negative vote, Young appointed a subcommittee to help NCI staff revise the concept statement. The BSA apparently was "unclear about what is new and inherent in this proposal, and what steps need to be taken to harvest the data out of the 10,000 people who have already been assembled," he said. "I suspect, if that came back with a clearer [statement] of what was going to be done in the next step, the vote might be different."

Curry agreed. "In the absence of discussion, the message that comes across is that this area of scientific inquiry is not supported, and I'm not sure if that's really the message that was being given," she said. "People need to be real clear, and that's why we have a BSA and why we have discussion, to get these issues out on the table. It's disappointing to me as a member… to have very little discussion and then a lot of people saying no without really clarifying what the issues were, it's hard to be clear going forward for folks at NCI. [CanCORS] is *the* study in cancer care outcomes. I think NCI should be doing this work."

Acting NCI Director John Niederhuber said the staff would take the board's vote "very seriously" and work with the subcommittee. "I think these types of studies are difficult to understand and somewhat difficult to present clearly so that everybody really understands the value of where we are going with it," he said.

In other action, the BSA approved the institute's plan to recompete four major clinical trials grant programs expected to cost a total of about $100 million over the next five years.

The board voted 20-0 with one abstention to continue one of the institute's longest-running phase I clinical trials programs, Early Clinical Trials of New Agents, which funds studies at 14 institutions.

Other programs the board approved included pediatric phase I trials, the American College of Radiology Imaging Network, and support for radiation therapy clinical trials. There were no votes in opposition to the initiatives.

The board voted 16-0 with five abstentions to approve the reissue of a Request for Applications for the Comprehensive Minority Institution/Cancer Center

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Partnership U54 cooperative agreements, expected to cost about $37 million over five years for three grants.

Excerpts from the concept statements follow:

Early Clinical Trials of New Anti-Cancer Agents With Phase I Emphasis. Concept for an RFA reissue, cooperative agreements, 14 awards, five years, first-year set-aside $8,263,605; total estimated cost $41,318,025. Program director: S. Percy Ivy, Division of Cancer Treatment and Diagnosis.

Since 1972, the Cancer Therapy Evaluation Program has managed an early therapeutics development program that has contributed to the clinical development of many anti-cancer agents. Through this program, hundreds of agents, both conventional and immunologic, have been made available for collaborative development. CTEP currently holds approximately 125 INDs for investigational agents. The Phase I U01 Program is critical for the initial phase of drug development. Many of the agents in NCI's portfolio are novel molecularly targeted agents that require more complex development than conventional agents. Pharmacodynamic assessment of drug effects on the molecular target has created the need for greater expertise in assay development, molecular imaging capabilities, tumor and specimen acquisition, and handling. This provides the foundation for rational therapeutics development.

Combination studies with molecularly targeted agents have become an increasingly high priority for NCI based on the clinical importance of these agents. Because of its extensive collaborations with industry, NCI is uniquely positioned to facilitate these important studies which are often difficult to negotiate in the private sector. NCI is currently sponsoring 104 trials with novel combinations, most placed during the past 2 years. Many of the initial phase I pilots of these combinations have been conducted in the phase I U01 program.

Specific accomplishments:

I) The U01 program funded 14 sites (Cancer Therapy and Research Center, Case Western Reserve University, City of Hope, Dana-Farber Cancer Institute, Duke University, Johns Hopkins Oncology Center, Mayo Clinic, Memorial Sloan-Kettering, Ohio State University, University of Pittsburgh, M.D. Anderson Cancer Center, University of Chicago, University of Wisconsin and Wayne State University). These sites provided the clinical expertise and infrastructure to conduct 185 clinical trials. During this funding period (2003-2005), 2,465 patients have been studied using 62 NCI-IND investigational agents and 112 investigational agent combinations.

From 2003-2005, investigators submitted a total of 295 LOIs. Of 70 unsolicited LOIs, 40 were approved. A total of 29 mass solicitations were also performed during this period resulting in 225 LOIs and 52 LOIs approved for protocol development. Overall, 31 % of solicited and unsolicited LOIs were approved between February 2003 and December 2005. During this period, a total of 79 trials were completed and 185 trials were ongoing in the U01 program; 135 (73%) were phase I, 13 (7%) were phase I/II, 35 (19%) phase II, and two were pilot studies (1%). Currently there are 112 active trials of 41 investigational agents and 67 combinations with an NCI investigational agent. The CTEP phase I U01 trials account for greater than 50% of phase I trials (excluding pediatric, CCR and others) performed under NCI sponsorship and all first in human studies were conducted in the U01s.

II) Scope of the phase I program: The agent classes studied include novel agents that target relevant cancer cell signaling pathways, as well as essential cellular machinery involved in the regulation of cell survival and apoptosis, proliferation and differentiation. Examples include tyrosine kinase inhibitors, EGF receptor inhibitors, angiogenesis inhibitors, mTOR inhibitors, farnesyl transferase inhibitors (FTI), cell cycle inhibitors, histone deacetylase (HDAC) inhibitors, proteasome inhibitors, heat shock protein inhibitors, PARP inhibitors, Src inhibitors, and novel cytotoxics, viral vector vaccines and immunotoxins. Types of agents under evaluation include small molecules, antibodies, vaccines, targeted toxins, anti-sense oligonucleotides, and gene transfer agents.

III) Evidence for agent activity in the phase 1 program: A number of agents deemed high priority by the DCTD's Drug Development Group for NCI sponsorship have been approved by FDA for licensing. During the most recent funding period, of the 62 agents studied, 30% have demonstrated clinical or target activity in phase I. Evidence of clinical activity was observed with cytotoxics such as rebeccamycin analog (hepatobiliary carcinoma) and epothilone B (breast and non-small cell lung cancer), HDAC inhibitors such as depsipeptide (cutaneous T-cell lymphoma) and MS-275 (myelodysplastic syndrome, and acute leukemia), Raf-kinase inhibitors such as BAY 43-9006 (sorafenib; renal cell carcinoma), cell cycle inhibitors such as flavopiridol (MDS and acute myelogenous leukemia), antiangiogenic immune modulators such as IL-12 (AIDS Kaposi's sarcoma) and farnesyl transferase inhibitors like tipifarnib (MDS and leukemia). NCI-sponsored agents in development by the phase 1 program that have achieved regulatory approval are: 1) imatinib mesylate; STI-571, Gleevec, gastrointestinal stromal cell tumors; Philadelphia chromosome + chronic myelogenous leukemia; 2) gefitinib (Iressa), NSCLC; 3) bortezomib (PS-341; Velcade), multiple myeloma; 4) oxaliplatin (Eloxatin), colorectal cancer, advanced, metastatic and adjuvant; 5) bevacizumab (Avastin), metastatic colorectal cancer, NSCLC, breast; 6) erlotinib (OSI-774; Tarceva), NSCLC; pancreatic; 7) 506U78 (nelarabine), T-cell ALL; T-cell lymphoblastic lymphoma and 8) sorafenib (Bay 43-9006; Nexavar): renal cell carcinoma.

IV) Evaluation of translational endpoints: The evaluation of future correlative studies in the U01 program will proceed in a judicious fashion through collaboration and with input from the Investigational Drug Steering Committee. The U01 program helped introduce tools to assess direct effects on molecular targets or their downstream effectors. These include: assessment of tumor tissue targets

(such as the effect of O^6 benzyl guanine on the suppression of methylguanine methyltransferase); demonstration of a direct effect of VEGF targeted therapy modulation on tumor interstitial fluid pressure; assessment of effects on peripheral blood mononuclear cells (PBMC) further defining dose and schedule; inhibition of ras farnesylation and oncogeneic/tumor survival pathways by tipifarnib; heat shock protein alterations by 17-AAG/17-DMAG that led to the assessment of alternative schedules when sustained target suppression was not observed; and ELISA-based PK assays that permit determination of cellular uptake and intracellular oligoneucleotide concentrations. Forty-three studies included tumor biopsies; 38 studies assessed target effects; 20 studies incorporated investigational imaging studies; and nearly all phase I trials have included pharmacokinetics.

V) Innovations from the phase I program:

Evaluating combinations of investigational agents—The pharmaceutical industry rarely tests investigational agent combinations because of intellectual property concerns. A strength and priority of the Phase 1 U01 Program is the study of investigational combinations. During this funding period, 31 investigational agent combinations have been tested. These trials have tested combinations of 1 CTEP-IND agent with commercial/older agents, or the combination of two CTEP-IND agents.

Dose determination/recommendations in patients with abnormal hepatic or renal function—A consortium of U01 sites organized to study the effects of anticancer drugs in patients with abnormal kidney and liver function has evaluated a number of IND agents including oxaliplatin, imatinib mesylate, bortezomib, epothilone B, and temsirolimus. Understanding the dosing for patients with hepatic or renal dysfunction allows these patients rapid access to new treatments, in which most U01 sites participate. Eight clinical trials over six years established the safe use of these agents in patients with excretory/metabolic limitations. These studies have been used in package inserts to provide guidance on the clinical use of oxaliplatin and imatinib in patients with impaired hepatic and renal dysfunction.

Novel phase I trial designs—Novel phase I trial designs including accelerated titration, Bayesian and other designs have been employed to optimize the number of patients receiving active doses of investigational therapeutics. Eighteen phase 1 studies using 10 investigational agents have explored the accelerated titration design and safely achieved their desired objectives.

Publications—Since 2003, 310 manuscripts from phase 1 trials or related studies supported by this cooperative agreement have been published. This represents an impressive increase compared to the 195 publications during the 5-year period of 1998-2002.

To address the critical areas of proficiency, the RFA will specify that the programs have the following components:

Research and Administration: Responsible for the scientific and medical expertise necessary to oversee multiple phase I single agent and combination studies under the leadership of the program principal investigator and the individual study chairs. It is required to develop protocols under strict time constraints. This component will be responsible for all regulatory communications and administrative duties including, but not limited to: development, tracking, distribution and filing of protocol amendments; filing adverse event reports defined in the FDA regulatory guidelines; toxicity reporting by dose and schedule for each protocol thereby assuring appropriate dose escalation and determination of recommended phase II dosing; auditing of associated sites for eligibility and study conduct compliance, and quality assurance and quality compliance of a regulatory nature; maintenance of all regulatory documents including 1572s and IRB approvals and communications; general tasks including site administrative duties and travel.

Data Management: Using three systems developed, used and maintained by CTEP including the Clinical Trials Monitoring System, the Clinical Data Update System, and the Adverse Event Expedited Reporting System.

Pharmacokinetic/Pharmacodynamic: The physicians, nurses, pharmacologists, and scientists responsible for the collection, distribution, analysis and reporting on the planned study pharmacokinetics and pharmacodynamic endpoints defined in the patient treatment protocols.

Clinical Trials Support: Each site will provide a description of the personnel that support the execution of the clinical trials including physicians, nurses, clinical research associates, pathologists, research pharmacists, institutional review boards and others: data collection, statistical support, data analysis, patient evaluation, and adverse event reporting.

The requested funding of $8,263,605 in FY08 represents a flat budget to support 14 awards, plus 5% increase in principal investigator salary to accommodate Investigational Drug Steering Committee participation.

The Pediatric Phase I/Pilot Consortium. Concept for an RFA reissue, cooperative agreements, 1 award, five years, first-year set-aside $3,305,379; total estimated cost $16,526,895. Program director: Malcolm Smith, DCTD.

NCI is the primary source of support for early phase evaluations of new drugs and new treatment approaches for children with cancer. The support that NCI has provided for early phase clinical trials has resulted in children with cancer having access to a broad range of new anti-cancer agents and has contributed to the identification of curative treatments for approximately 80% of children with cancer. Nonetheless, 20% of children with cancer succumb to their disease, and a significant number of survivors experience significant short- and long-term toxicities. Particularly troubling is the leveling off of childhood cancer mortality rates from 1998-2003, following over 30 years of steady annual declines in the childhood cancer mortality rate. It is essential that new agents and new treatment approaches be safely introduced and thoroughly evaluated in children so that a new era of discovering more effective treatments for children with

cancer can be initiated and so that children can benefit from the advances in cancer, biology and drug development that are revolutionizing the treatment of cancer in adults. The proposed recompetition, therefore, represents a continuation of NCI's historic commitment to childhood cancer research as well as a forward-looking program for extending targeted therapeutics into the pediatric population.

The recompetition of the RFA for the Pediatric Phase l/Pilot Consortium builds upon experience during the first funding period of the COG Phase l/Pilot Consortium and is based on the following nine principles:

1) Single institution pediatric phase 1 studies are generally not feasible due to limited patient numbers, and excessive numbers of institutions participating in phase 1 trials is inefficient as well as sub-optimal in terms of monitoring and assuring patient safety. To conduct phase 1 studies in children, it is essential to have a limited number of experienced institutions with proven patient accrual capabilities.

2) Timely development and implementation of phase 1 studies and pilot studies is essential to applying advances in cancer biology and drug development to the pediatric setting. This requires committed investigators as well as experienced protocol development staff and efficient protocol development procedures, with clearly defined timelines for completion of each step in protocol development and implementation.

3) Data from pediatric phase 1 and pilot studies must be of the highest quality and must be submitted in a timely manner. This requires committed, trained staff at local institutions, effective mechanisms for data collection and analysis, and mechanisms for onsite audits to verify reported data and to assure protocol compliance.

4) Correlation between agent dose and biological effect is important for new agents with specific molecular targets, but ethical considerations limit the extent to which tumor sampling that is strictly for research purposes can be employed. The Consortium must be able to employ alternative methods to gain important information relevant to targeted agent evaluation (e.g., studies of surrogate tissues, noninvasive imaging, etc.).

5) Pharmacokinetic studies are central to pediatric phase 1 trials, as they allow comparison to systemic exposures achieved in adult patients and in pediatric preclinical models. In both adults and in preclinical models, relationships between systemic exposure and target modulation can be demonstrated, thereby providing benchmarks for the drug levels and systemic exposures that should be targeted in children.

6) Imaging methods have great potential for determining the effect of agents on target tissues, and the Consortium should apply state-of-the-art imaging methods to pediatric drug development. This requires staff and resources for central collection, analysis and archiving of research images, and it also requires the capability and commitment of participating institutions to perform imaging studies in the protocol-prescribed manner.

7) Pilot studies of promising multi-agent regimens (which may or may not involve a dose escalation) are a key step in the integration of new agents into the therapy of specific childhood cancers and require careful monitoring for toxicity and safety such as can be provided by the Consortium's member institutions. Development and conduct of pilot studies requires close, coordination with COG.

8) Institutional members of the Consortium should be selected and maintained as members based upon objective criteria and upon an impartial assessment of their ability to contribute both scientifically and through patient accrual to the Consortium.

9) Drug development for children with cancer should be a public-private partnership. Excessive reliance on pharmaceutical support increases the risk that new agents will be prioritized for evaluation in children based on their potential market size for adults with cancer, rather than on the scientific rationale justifying their potential benefit to children. Pharmaceutical support should enhance, rather than supplant, the NCI-supported infrastructure for safely and expeditiously evaluating the most promising new agents for the treatment of children with cancer.

The majority of phase 1 trials for children with cancer over the past 10-15 years have been conducted by the COG Phase 1 Consortium or its predecessors, the Pediatric Oncology Group Phase 1 Consortium or the Children's Cancer Group Phase 1 Consortium. The POG and CCG Phase 1 Consortia were initially funded in September 1992, and the COG Phase l/Pilot Consortium was initially funded in August 2002.

The COG Phase l/Pilot Consortium has made numerous contributions to new agent development for children with cancer during its first 3 years of funding. A measure of the productivity of the Consortium is the number of agents that have entered pediatric evaluation to date in its first funding period: 20 phase 1 or pilot protocols have been activated (or are nearing activation). The Consortium activated 6.5 new clinical trials per year in the two most recent years (FY2004 and FY2005). At any given time, 10-12 Consortium trials are active. For most of these studies, pharmacokinetic analyses are performed, providing an important source of data concerning agent disposition and metabolism in children and setting the stage for limited sampling pharmacokinetic approaches in subsequent trials. Accrual to Consortium studies has steadily increased during the Consortium's first funding period, from 78 in FY2003, to 107 in FY2004, and to 129 in FY2005. As procedures are implemented to facilitate development and conduct of pilot studies by the Consortium, the accrual should continue to increase to meet or exceed the target 200 enrollments per year.

An important accomplishment of the Consortium during its first five-year funding period was the establishment of a center for the electronic collection and analysis of imaging studies performed at its 20 member institutions. This capability is essential if the Consortium is to apply state-of-the-art imaging methods to its early phase clinical trials. The imaging center was selected in a competitive process with input from the NCI Cancer Imaging Program.

The successful applicant from Children's Hospital of Los Angeles has established electronic connectivity with the Consortium's member institutions that allows the submission of complex imaging studies, and imaging objectives have been incorporated into recent Consortium protocols. In the short term, the imaging center will allow the consortium to utilize dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) to evaluate anti-angiogenic agents in children. In the future, the center should allow the consortium to incorporate other imaging methods into its studies of molecularly targeted agents (e.g., MRI with macromolecular contrast agents, magnetic resonance spectroscopy, PET imaging, etc.).

The Consortium has incorporated pharmacodynamic evaluations, in addition to pharmacokinetic studies, into many of its clinical trials. Examples include: Demonstrating accumulation of acetylated H3 histones in peripheral blood mononuclear cells in children receiving the histone deacetylase inhibitor depsipeptide. Demonstrating Hsp72 induction in PBMCs as a marker for inhibition of Hsp90 in children receiving 17-AAG. Demonstrating immune activation/modulation in children receiving Hu14.18-IL2 (humanized 14.18 antibody genetically linked to a molecule of human IL2) as evidenced by elevated serum levels of soluble IL-2 receptor alpha (sIL2Ralpha) and lymphocytosis, and demonstrating an antibody response against the idiotypic and the Fc-IL2 components ofHu14.18-IL2. Quantitating plasma VEGF levels and circulating endothelial cell (CEC) and circulating endothelial cell precursors (CEP) in children receiving bevacizumab. Quantitating plasma circulating levels of epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), and matrix metalloproteinases (MMP)-2 and -9 in children receiving gefitinib, and demonstration of absence of EGFR mutation in a responding patient with Ewing sarcoma.

The Consortium monitors the performance of its members in terms of patient accrual, timeliness and quality of submitted data, and scientific contribution. One institution has been dropped from the Consortium for poor performance. To ensure that the Consortium is dynamic and that its institutions are among the most capable in North America for conducting early phase pediatric clinical trials, the Consortium will compete the membership of those institutions in the lower tertile of performance. This will allow capable institutions that are not currently members of the Consortium to contend for one of the Consortium's 20 membership slots.

Phase II studies are either ongoing or in late stages of development for pemetrexed, bortezomib, bevacizumab, the antibody-cytokine conjugate HU14.18-IL2, ecteinascidin-743 (Y pndelis), motexafin gadolinium (gadolinium texaphyrin), and for the erlotinib and temozolomide combination.

The Consortium had 27 publications from the past 3-4 years and six Consortium abstracts were presented at the 2006 ASCO meeting describing the early experience in children for bevacizumab, erlotinib, pemetrexed, 17 -AAG, bortezomib, and motexafm gadolinium.

To accomplish the objectives of the RFA, a strong multi-disciplinary research team is needed that can rapidly and efficiently design and conduct phase I and pilot clinical trials and that is experienced in doing this within the ethical constraints that apply to research involving children.

The RFA will specify that the Phase l/Pilot Consortium have the following components:

—Strong scientific leadership is essential for prioritizing new agents for evaluation and for directing the development and implementation of scientifically and clinically sound phase I and pilot studies in children with cancer. Expertise in pharmacology, translational research, and imaging is also required.

—The Research Administration Component is responsible for meeting the administrative, financial management, and regulatory needs of the Consortium. This component will prepare and distribute protocol documents and amendments, arrange Consortium meetings, assure compliance with FDA and OHRP regulatory and patient protection requirements, coordinate manuscript development, and monitor performance of institutional members. The Research Administration Component will also provide reports on the performance of the Consortium in meeting pre-specified timelines for LOI concept and protocol development, for study implementation, and for publication of studies. This component must also have financial management capabilities to ensure timely reimbursement of institutions and laboratories for Consortium-related activities.

—Member institutions should have documented experience in participating in phase I trials and should have the requisite highly qualified medical, nursing, and pharmacy staff. Institutions should have demonstrated ability to carefully monitor patients treated on phase I and pilot studies, to report clinical data in a timely manner for central collection and review, to contribute to the scientific leadership of the Consortium, and to employ state-of-the-art imaging studies in the phase I setting. The Consortium should have no more than approximately 20 institutions, a number that should be sufficient to complete approximately 5-6 phase I trials per year (120-140 patients) and to complete a smaller number of pilot studies per year (60-80 patients). Procedures should be in place for COG institutions that are not Consortium members to participate in selected Consortium trials if they have unique capabilities needed to complete a particular trial or if they have contributed significant scientific leadership in the development of a new agent under investigation.

—The Data Management and Analysis Component will be responsible for data management and data analysis and for the overall statistical needs of the Consortium (e.g., developing analysis plans and analyzing data during and after completion of protocol accrual). The use of a remote data entry system will be required.

—The Pharmacokinetic/Pharmacodynamic (PK/PD) Component will be responsible for integrating pharmacokinetic and pharmacodynamic endpoints into the Consortium's clinical trials. This allows key PK parameters to

be compared between adult and pediatric patients to identify evidence of age effects and to determine how data from adult studies relating systemic exposure to target modulation can be applied in the pediatric setting. This component will design and conduct correlative studies to determine relationships between dose, PK parameters, and biological effects of the administered agent. It will also include the Consortium's imaging resources responsible for the central collection, review, and archiving of research imaging studies. These studies will be focused on relating imaging correlates of drug effect to PK and clinical parameters.

Budget Considerations: The COG Phase I/Pilot Consortium in FY2005 (Year 4) has committed direct costs of $2,917,459 and F&A costs of $301,300, which gives a total approved budget of $3,218,759. The committed funding level for FY2006 (Year 5) is $3,305,379. The proposed funding for the RFA is based on no increase. An approximate distribution of funds into major categories is provided below:

—Scientific Leadership (Total: $300,000): The Consortium's Scientific Leadership includes the Chair and Vice-Chair (20-25% effort), medical director of protocol development (10% effort), and pharmacology chair (10% effort).

—Regulatory & Administration Component (Total: $360,000): $230,000 to support the activities of the Regulatory & Administration Component related to overall project management and coordination, protocol development and implementation, and QA/QC. $130,000 to cover travel to the COG semi-annual meeting for institutional PIs and study chairs, travel for clinical research associates to one meeting per year for training, and travel for the Consortium leadership to meet with NCI.

—Data Management and Analysis Component (Total: $240,000): $240,000 for data management and analysis, statistical support, and information technology support.

—Basic Site Support (Total: $1.2 million): Basic site support is organized into three categories, non-accrual-related activities, accrual-related activities, and special research tests performed at the institution. $500,000 ($25,000 per institution) to support approximately 5% PI time and 15-20% CRA time. These funds support the non-accrual based responsibilities related to participating in the Consortium's clinical trials that must be met whether patients are ever enrolled on a study at an institution. $400,000 for per capita accrual, based on approximately $2,000 per case for 200 cases. $300,000 for institutional costs of research that are not considered a cost of treatment by medical insurers, and therefore not reimbursed.

—Pharmacokinetic and Pharmacodynamic Component (Total: $775,000): $400,000 to support laboratories that conduct correlative studies (e.g., pharmacokinetics and translational biology studies). $375,000 to support the Imaging Research Center.

American College of Radiology Imaging Network. Concept for a letter RFA to maintain the current network, two awards, five years, first-year set-aside $7.3 million; total estimated cost $38.755 million. Program director: Barbara Galen, DCTD.

The American College of Radiology Imaging Network was created to establish a flexible, responsive, multi-center network for the systematic study and-facilitation of the development and rigorous assessment of technologies relevant to the imaging of cancer.

ACRIN is entering its eighth year of funding and is in its second funding cycle (1999-2003 and 2004-2007). In response to a competitive RFA issued in 1997, ACRIN has been funded since March 1, 1999. ACRIN is a consortium of two separate U01's [U01CA80098 (Headquarters) Bruce Hillman, Principal Investigator, American College of Radiology and U01CA79778 (Biostatistics and Data Management Center) Principal Investigator, Brown University].

ACRIN has undergone several reviews, internal and external, over the past seven years. In general, each review found ACRIN to be positioned at an appropriate level of progress for an evolving cooperative group. ACRIN was last competed using the Letter RFA mechanism in 2003. The NCI site review committee in July 2003 rated both applications very good overall. Recently, a Mid-term Review (December 7, 2005) was conducted by an internal/external ad hoc NIH committee. These reviewers commented on ACRIN's competence, vision, progress and relevance as reflected in ACRIN's presentation of a clear and relevant scientific agenda; enhanced organizational structure; formalized decision making processes; provision of image and meta-data archives for secondary research and education; realistic and effective quality assurance and quality control programs that are tailored to imaging science; enhanced integration between ACRIN Headquarters and the Biostatical Data Management Center; and enhanced integration/collaboration with the clinical oncology, industry, regulatory, and ancillary science communities.

ACRIN has succeeded in establishing an intrinsically collaborative, multi-disciplinary network composed of physicians, scientists, methodologists, industry, and patient advocates. They are an electronically managed and operated network with electronic case report forms; 24 x 365 registrations; randomization; image and data transmission; and archive. This initiative will support the maintenance and further development of a unique, multi-center imaging network.

Advanced Technology Radiation Therapy Clinical Trials Support (ATC Consortium). Concept for a letter RFA, cooperative agreement, 1 award, five years, first-year set-aside $1.75 million; total estimated cost $8.75 million. Program director: James Deye, DCTD.

This RFA is to continue support for the Advanced Technology Radiation Therapy Clinical Trials Support initiative. In 1998, the Radiation Research Program solicited applications for projects that would generate a resource that uses state-of-the-art methods to develop quality assurance

criteria for NCI sponsored high technology radiation therapy clinical trials and to implement those criteria for selected clinical protocols when applicable, including credentialing of participating institutions and treatment plan review.

Two grants were funded: one at Washington University in St. Louis [the Advanced Technology Consortium (ATC) for coordination, integration and development of review tools for archiving and credentialing] and the other at the University of Florida in Gainesville [the Resource Center for Emerging Technologies (RCET) fro development of web based, self-anonymizing software tools].

After the initial three-year funding period, this initiative was re-competed by means of a letter RFA and the original two awardees were again successful. However, it was felt that there was less need for developmental work and more need for integration of existing technologies into the QA infrastructure, hence most of the funding of the developmental effort at University of Florida was accomplished by means of a subcontract under the ATC, while a small U24 development component continued at the RCET. It is recommended that only one award be made to continue integrating these service and developmental efforts into the various clinical trials through the ATC. There are many quality assurance, data transfer and database needs since these technologies are still being assimilated into routine clinical use. Several clinical trials groups are in the process of activating clinical trials that will utilize advanced technologies that require the ongoing support and participation of the awardees. Specifically, there is continuing need for: 1) QA and credentialing as part of the growing number of complex 3- and 4-D conformal and IMRT based clinical radiation therapy trials, 2) increased cooperation among the clinical trial QA efforts especially in the area of uniform credentialing and benchmarking, 3) increased implementation of DICOM RT data exchange standards including vendor-specific capabilities, 4) increased uniformity in archiving and database methodologies so that data mining relative to patient outcomes may be realized and 5) further development of phantoms to test the efficacy and quality of proposed complex treatment methodologies.

Comprehensive Minority Institution/Cancer Center Partnership. Concept for an RFA, cooperative agreement, 3 awards, five years, first-year set-aside $7.5 million; total estimated cost $37.5 million.

The first MI/CCP cooperative agreements (U56/U54) were awarded in 2001. This concept asked minority-serving institutions and NCI-designated cancer centers to combine their experience to 1) produce more competitive grant funding from minority investigators in cancer research, training, education, and outreach, 2) increase the competitive research capacity at MSIs, 3) increase cancer outreach from cancer centers in minority communities, and 4) enhance research at the cancer center directed in cancers that disproportionately affect and burden racial, ethnic minority, and underserved populations. The U54 grant must address cancer research, training, and outreach; cancer education is optional.

In Brief:

No-Smoking Policy Adopted At Roswell Park Campus

(Continued from page 1)

announced it will be the first hospital in Western New York to adopt a campus-wide no smoking policy, said **Donald Trump**, senior vice president for clinical affairs. The policy applies to all institute employees, patients, visitors, students, trainees, volunteers and vendors with the exception of those involved in smoking-related studies. Support is being given through smoking cessation programs, nicotine replacement products and counseling from the New York State Smokers Quit Line. Roswell Park worked with several organizations to establish the policy, including the American Cancer Society, Buffalo-Niagara Medical Campus, Erie-Niagara Tobacco-Free Coalition, the Public Employees Federation, Civil Service Employees Association, and the New York State Correctional Officers & Police Benevolent Association. . . . **CANCER THERAPY AND RESEARCH CENTER** of San Antonio appointed two scientists to its staff, said **Karen Fields**, president and CEO of CTRC. **Salvador Bruno** has joined as a research physician in the Hematology and Oncology Division. He also serves as a clinical associate professor in the Department of Medicine at the University of Texas Health Science Center at San Antonio. Bruno, who was associate professor of medicine and medical director of oncology services at the Medical College of Georgia, will expand the lymphoma and myeloma programs at CTRC. **Chee Ng** has joined as director of pharmacokinetics and pharmacodynamics at the CTRC Institute for Drug Development. Ng also was appointed assistant member of the IDD, reporting to **Chris Takimoto**, director of pharmacology. He has an appointment as clinical assistant professor of pharmacology at the University of Texas Health Science Center at San Antonio. Ng, who was a scientist in the clinical and experimental pharmacology department at Genentec, will be involved in the education of the IDD physician fellows and trainees in drug development on the topic of clinical pharmacology and pharmacokinetics and pharmacodynamics . . . **MITCHEL BERGER**, professor and chairman of neurosurgery and director of the Brain Tumor Research Center at the University of California, San Francisco, delivered the Ronald L. Bittner Lecture April 24 at the American Association of Neurological Surgeons annual meeting in San Francisco. His lecture summarized the advances of the UCSF Brain Tumor SPORE grant.

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