

Board of Scientific Advisors

Meeting Minutes
September 22-23, 1998
The Palladian Room
Omni Shoreham Hotel
Washington, D.C.

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The Board of Scientific Advisors (BSA), National Cancer Institute (NCI) convened for a *Special Session* and its 9th meeting at 6:30 p. m. on Tuesday, September 22, 1998, in the Palladian Room, Omni Shoreham Hotel, Washington, D.C. Dr. David Livingston, Professor of Medicine, Dana-Farber Cancer Institute, presided as the Chair.

The meeting was open to the public from 6:30 p.m. until adjournment on Wednesday, 23 September, for introductory remarks from the Chair, ongoing and new business, and presentations and discussion of reports from the Tobacco Research Implementation Group (TRIG), Clinical Trials Implementation Committee (CTIC), and Developmental Therapeutics Program Review Group (DTPRG).

BSA members present:

Dr. David Livingston (Chair)
Dr. Frederick R. Appelbaum
Dr. Mary Beryl Daly
Dr. Virginia Ernster
Dr. Suzanne W. Fletcher
Dr. E. Robert Greenberg
Dr. Waun Ki Hong
Dr. Tyler Jacks
Ms. Amy S. Langer
Dr. Caryn E. Lerman
Ms. Deborah Mayer

Dr. Enrico Mihich
Dr. John D. Minna
Dr. Nancy E. Mueller
Dr. Sharon B. Murphy
Dr. Stuart L Schreiber
Dr. Joseph V. Simone
Dr. Peter K. Vogt
Dr. Daniel D. Von Hoff
Dr. Robert C. Young
Dr. Elias A. Zerhouni

BSA members absent:

Dr. Joan Brugge
Dr. Eric R. Fearon
Dr. David D. Ho
Dr. Herbert Y. Kressel
Dr. Joan Massague
Dr. W. Gillies McKenna
Dr. Allen I. Oliff
Dr. Franklyn G. Prendergast
Dr. Louise C. Strong
Dr. Barbara L. Weber
Dr. Alice S. Whittemore
Dr. William C. Wood

NCAB liaison Absent:

Dr. Philip A. Schein

Others present included: Members of NCI's Executive Committee (EC), NCI staff, members of the extramural community, and press representatives.

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CALL TO ORDER AND OPENING REMARKS - DR. DAVID LIVINGSTON

Dr. David Livingston called to order the 9th and special meeting of the Board of Scientific Advisors (BSA or Board) and welcomed members of the Board, National Institutes of Health (NIH) and National Cancer Institute (NCI) staff, guests, and members of the public. Dr. Livingston introduced and welcomed newly appointed Board member Dr. Elias A. Zerhouni, Professor and Chairman, Department of Radiology, The Johns Hopkins University School of Medicine.

CONSIDERATION OF JUNE 1998 MEETING MINUTES - DR. DAVID LIVINGSTON

A motion to approve the minutes of the 8th meeting of the Board of Scientific Advisors, which was held on June 22-23, 1998. The

motion was seconded and unanimously approved.

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TOBACCO RESEARCH IMPLEMENTATION PLAN - DR. BARBARA RIMER AND DR. CARYN LERMAN

Dr. Barbara Rimer, Director, Division of Cancer Control and Population Sciences (DCCPS), informed BSA members that the Tobacco Research Implementation Plan builds on the recent reports of the Institute of Medicine's (IOM) National Cancer Policy Board (NCPB) and NCI's Prevention and Cancer Control Program Review Groups (PPRG and CCPRG, respectively). Developed by the Tobacco Research Implementation Group (TRIG), the TRIP proposes a comprehensive agenda that considers the entire spectrum of tobacco control research from basic biological to dissemination research. The full written report will be available at the November BSA meeting.

Background. The TRIG Chair, Dr. Caryn Lerman, Professor of Medicine and Psychiatry, Georgetown University Medical Center, reported that tobacco is responsible for 30 percent of cancer deaths. The trend in data showing the prevalence of cigarette smoking among adults has leveled since 1990 after exhibiting a steady decline in the previous 35 years, suggesting the need for more innovative therapies to promote smoking cessation. Moreover, smoking among American youth, beginning as early as eighth grade, has been on the rise in the past few years. NCI's special tobacco initiatives since 1983 included projects targeted to specific high-risk groups and large-scale intervention trials such as the Community Intervention Trial for Smoking Cessation (COMMIT) and the American Stop Smoking Intervention Study (ASSIST). Recently, research has focused on tobacco policy and the efficacy of pharmacologic and behavioral interventions for smoking cessation. Responses to recent BSA approved Requests for Applications (RFAs) for basic biobehavioral and health communications research suggest that tobacco-related research will form a significant component of the NCI grants portfolio.

In spite of the progress that has been achieved through past and

current initiatives, a number of questions remain. Thus, the TRIG was convened to review the NCI research portfolio in tobacco, specifically to determine the priorities for tobacco-related research for the next 5-7 years. The portfolio analysis research categories formed the framework for the recommendations. Recommendation criteria were 1) research focus; 2) increase the understanding of tobacco addiction, initiation, and cessation process; 3) exert a major impact on tobacco use prevention; 4) increase substantially the effectiveness of nicotine addiction treatments; 5) exert a major public health impact on population smoking rates; 6) provide a balance of long- and short-term investments; and 7) provide a balance across research categories.

Dr. Lerman stated that TRIG members unanimously concluded that an unequivocal commitment to a comprehensive, focused approach to research on tobacco use could reverse the existing epidemic of tobacco-related cancers.

TRIG recommendations: 1) Creation of *multidisciplinary centers* for the study of initiation and prevention of tobacco use, addiction to tobacco, and/or treatment of tobacco addiction and tobacco-related cancers; 2) *basic biobehavioral research* to understand the interactions of sociocultural, psychological, and genetic factors that influence the initiation of tobacco use, progression to nicotine addiction, and smoking cessation among children, adolescents, and adults. A particular focus would be on young adults; 3) Research on the *treatment of nicotine addiction* to find the best ways to tailor tobacco cessation interventions to specific sociocultural, psychological, physiological, and genetic subgroups; 4) Research to improve *community and state tobacco control programs* and to understand their impact on populations at disproportionate risk; 5) Research to identify mechanisms for optimal *dissemination* of proven prevention and treatment interventions; 6) Research to understand the impact of *tobacco policies*, including taxation and pricing, clean indoor air policies, marketing restrictions, youth access restrictions, and new tobacco product and nicotine replacement regulation; 7) Basic biological research to identify and validate *biomarkers* of tobacco exposure and markers of early stages of carcinogenesis; 8) Research to understand *genetic and environmental interactions* in susceptibility to tobacco-related cancers to identify subgroups at risk; and 9) Research on expanded *surveillance* systems to monitor tobacco use behaviors, the implementation and fidelity of tobacco-related interventions, and

other factors that influence tobacco use.

As a first focus for NCI action to address the recommendations, the TRIG encourages the continued expansion of the tobacco portfolio through investigator-initiated research, cancer centers, collaboration across the NCI, with other Institutes, agencies, foundations, organizations, and corporations. The TRIG also proposed several special initiatives or Request for Applications (RFAs) for fiscal year (FY)1999 and FY 2000, including: 1) research to improve state and community tobacco programs; 2) establishing tobacco research centers; 3) epidemiological studies; 4) research on the treatment of nicotine addiction; 5) expanded surveillance research; and 6) basic biobehavioral research. NCI has already begun addressing the problems of youth and tobacco through the release and re-release of an RFA. New mechanisms for training cancer control scientists should be developed to provide training in the multidisciplinary aspects of tobacco control research.

In discussion and in response to questions, the following points were made:

- When asked if studies on the mechanism of cigarette carcinogenesis at a molecular level had been proposed, members were told that the recommendation on basic biology and carcinogenesis would address that research area.
- The DCCPS has begun exploratory conversations with the World Bank and other international groups working on tobacco to identify potential partners to participate in NCI tobacco initiatives.
- The NCI is committed to reinvesting the portion of the budget currently funding the ASSIST study in the area of tobacco control research.
- The tobacco centers would be modeled on the Specialized Programs of Research Excellence (SPORES) with collaborations among biologists, epidemiologists, and behavioral scientists.

- NCI's commitment to fund the initiatives recommended in the TRIP extends beyond the reinvestment of the funds currently allocated to the ASSIST Program. Cost projections for implementing the TRIP recommendations are \$5M for basic biobehavioral research; \$5M in supplements to existing or new cohorts to study the process of initiation among children; \$3M for new treatment research; \$20M for community and state intervention research; and \$5M for multidisciplinary centers. These expenditures are expected to fit within the growth of the NCI budget from the appropriations process, without any expectations in terms of a windfall from tobacco legislation.
- In those states where tobacco litigation has provided extra funding, many of the policy initiatives at the statewide level have the potential to be good national laboratories for some of the policy research that is proposed in the TRIP.
- To appropriately communicating NCI's tobacco research priorities to the public, the executive summary should be enhanced to include the priorities in the areas of youth and tobacco, training, research involving former smokers, and passive smoking.
- Gender, ethnic, and racial differences and changes in types of lung cancer are areas where the changes in trends are not understood. Women are not identified in the full report as a group at necessarily higher risk because, in all ethnic groups, both smoking prevalence and lung cancer rates are higher in men than women. Lung cancer rates have plateaued and started to decline in men.
- An ongoing dialogue exists between the NCI and American Cancer Society (ACS) on tobacco issues; in particular, the ACS intervention agenda is well known and is a focus of collaboration between the two institutions.
- When queried about the Breast and Prostate Cancer Progress Review Group reports, staff indicated that the reports will be presented at the November 1998 meeting.

REPORT OF THE DIRECTOR, NCI - DR. RICHARD KLAUSNER

Dr. Richard Klausner, Director, NCI, thanked BSA members for agreeing to attend a special meeting convened to solicit advice and guidance on three important reports, the Tobacco Research Implementation Plan, Clinical Trials Implementation Group recommendations, and the Developmental Therapeutics Program Review Group report. Dr. Klausner described the meeting as a milestone in view of the fact that five major reviews of NCI programs, initiated 3 years previously as requested by the BSA, will be completed with the presentation of the DTPRG report. These five reports will continue to guide the restructuring of major NCI infrastructures and major areas of research to integrate science into the goals of the National Cancer Program (NCP). Board members were reminded that the PRG reports signal the initiation of a process that begins with the creation of implementation groups which are charged with producing research agendas that will effectively implement the recommendations of each PRG.

FY 2000 and FY 2001 Bypass Budgets. Members were reminded that the NCI has been guided in its priority setting by the annual Bypass Budget. *The Nation's Investment in Cancer Research: A Budget Proposal for Fiscal Year 2000* includes the list of extraordinary investment opportunities identified for the first 3-year cycle that began in FY 1997. The NCI is beginning to develop a new set of extraordinary opportunities to be included in the second cycle that begins with the FY 2001 Bypass Budget. All advisory boards, NCI staff, grantees, cancer center directors, professional society members, and advocacy groups will be sent participation guidelines to be used in identifying extraordinary investment opportunities for the new cycle.

Dr. Klausner gave an overview of the importance of understanding the overall scope of NCI initiatives, the relationship of initiatives for which the BSA provides oversight, and the degree to which the NCI articulates its priorities and acts on them. He informed members that the challenge is to ensure that Congress, the National Cancer Advisory Board (NCAB) in its oversight role, the public,

and the research community understand how the NCI plans, prioritizes, and implements initiatives for making progress against the diseases for which it has responsibility, and that these constituencies are aware of the opportunities for participation. The four extraordinary investment opportunities included in the current Bypass Budget are Cancer Genetics, Signature of Cancer Cells, Preclinical Models, and Detection/Imaging. Members were given a brief overview of each of the extraordinary opportunities. Specifically, 1) **Cancer Genetics** includes the:

Cancer Genetics Network - a new national resource that provides the infrastructure, linked by state-of-the-art informatics, to conduct a broad range of collaborative research on cancer genetics and translate research findings to change the practice of both preventive and therapeutic oncology, as well as to address the psychosocial, ethical, and legal issues associated with inherited cancer susceptibility. Eight participating centers are in operation covering the Mid-Atlantic, Southeast, Southwest, and West Coast.

Cooperative Family Registries for Breast and Colorectal Cancer Studies - a comprehensive, collaborative infrastructure, linked to an informatics structure, to help speed the genetic and epidemiologic study of heritable cancers. Twelve participating institutions are located in the United States, Canada, and Australia. The Cancer Genetics Working Group will be reconvened in December to determine whether these registries are optimally structured to provide the resources needed to answer questions about cancer predisposition for the entire research community. The BSA will receive a report of the results of the meeting.

Cancer Center Supplements - awarded in FY 1996 to stimulate the development of resources and pilot projects in human cancer genetics. Included in the accomplishments to date are 23 funded research projects, many of which have resulted in peer review funded grants.

Genetic Annotation Initiative (GAI) - a research program to explore and apply technology for the identification and characterization of genetic variation in genes important to cancer. One goal for the next year is to have at least 3,000 genes associated with polymorphisms in the CGAP GAI Web site. Cancer Chromosome Aberration Project (CCAP) - designed to develop technologic tools that will allow for the definition and detailed

characterization of the chromosomal alterations that are associated with malignant transformation. A repository of genetically and physically mapped DNA bacterial artificial clones (BAC) anchored across the human genome will be generated. A database will be developed to display the repository in an accessible and meaningful format and provide a platform for correlation with parallel databases of cancer-associated chromosome aberrations and clinical, histopathologic information. The goal is to integrate the analysis of cytogenetic changes by using new approaches such as spectral karyotyping and comparative genomic hybridization to look for amplifications or deletions. A new nomenclature is being developed for the description of chromosomal abnormalities, which will be published and then made available on the NCI Web site linked to a repository of actual clones.

2) **Signature of Cancer Cells** consists of the *Cancer Genome Anatomy Project (CGAP)* - the comprehensive molecular characterization of normal, precancerous, and malignant cells. Information on new genes is made available immediately in the CGAP Web site. During the past year CGAP gene discovery, a collaborative effort involving extramural and intramural scientists and industry, has been adding more than 300,000 gene sequences and about 11,800 new genes-about 20 percent of all known genes-to the public database. This high discovery rate was attributed to the development of technology, such as microdissection, to obtain high-quality libraries. Significant progress has been made in gene discovery in the five tumor sites (breast, colon, lung, ovary, and prostate) targeted for the first year and validation of these discoveries is proceeding; *Tissue Resources* is a new program on the internet, **the NCI Tissue Expediter**, was developed to match investigators with appropriate resources. In addition, a new PA will foster the linkage between investigators and the cooperative groups; and *Phased Innovation Awards* - provide a funding mechanism for developing and testing new technologies that underlie discovery in all aspects of cancer research. Other initiatives are the *Development of High-Throughput Analysis* program announcements and request for applications;

Dr. Klausner issued a Director's Challenge to the research community to use the available technology development funding and all the new sources of information to develop a new set of tentative diagnostic and classification schemes for all major tumors during the next few years.

3) **Preclinical Models** of cancer discussions have resulted in a Mouse Models of Human Cancer Consortium RFA. This RFA is expected to make possible the systematic funding of model development and dissemination and connection of developers of models to the evolving technologies and resources that are needed. Plans are to provide supplements to investigators to support the added cost of maintaining animal models. Other projects are the Mouse CGAP and the Mouse Genetic Mapping Initiatives.

4) **Detection/Imaging** includes the *Diagnostic Imaging Network* - a national infrastructure will be established for multi-institutional clinical trials and the rapid identification and assessment of innovative imaging technologies. Additionally, the *Small Animal Imaging Resource Programs* (SAIRPs) will provide both an imaging resource to oncology researchers and a laboratory for research and development of small animal imaging technologies, in particular, functional imaging. A proposal to support the creation of centers for functional imaging will be brought to the BSA. Also in the planning stages is a high-priority proposal that would create a *National Detection Research Network* for collaborative research on molecular, genetic, and other biomarkers in human cancer detection and risk assessment. Another diagnostic/imaging project will be undertaken as part of NCI's *Unconventional Innovations Program*, with the scientific goal of creating a common platform for noninvasive integrated detection, diagnosis, and therapy based on molecular profiles of cancer. Through the NCI Web site, suggestions are being solicited from the scientific community about technological opportunities that would further the stated goal.

After concluding his overview on how initiatives and funding mechanisms are created to respond to scientific opportunities identified through NCI planning processes, the need for a collaborative effort between the NCI and BSA to ensure that the public understands what scientific opportunities are available and how to access information on resources and funding mechanisms was emphasized. Members were encouraged to respond to the request for suggested new extraordinary investment opportunities, with the assurance that the list ultimately chosen will guide future investment.

In subsequent discussion and in response to questions, the following points were made:

- Additional information on the CGAP Web site was requested. Information on the numbers of requests and the types of users who are accessing the site should be included.
- In an effort to develop support for the NCI and in communicating the National Cancer Program, the November BSA meeting working lunch discussion should focus on the NCI and the BSA developing a booklet/ document for distribution to the general public describing and explaining NCI activities and efforts.
- When queried about patient social concerns that could have an impact on NCI's scientific effort, the Board was told that the latest published figures show that the U.S. public strongly supports scientific research even if that research does not have an immediate benefit. However, another segment of the public looks for immediate outcomes, and a range of other issues appear such as global fears about cloning or food alteration or personal fears in terms of medical information. NCI's responsibility, therefore, is to address the entire range of perceptions. The difficulty occurs in trying to gauge the current public view in support of the promise of scientific research and how tightly it is linked to immediate results. An important goal is to engage the public in both the Institute's values in terms of the necessity of discovery to progress against disease and the Institute's awareness of the personal and social implications of its discoveries.
- A major responsibility of the BSA and the NCI is the communication of all of these new initiatives, funding mechanisms, and resources. The information exchange should begin early in the training of new investigators, even down to the level of graduate students.

**CLINICAL TRIALS IMPLEMENTATION COMMITTEE
REPORT - DR. ROBERT WITTES, DR. JOHN GLICK, AND
DR. MICHAELE CHRISTIAN**

Dr. Robert Wittes, Deputy Director for Extramural Science (DDES) and Director, Division of Cancer Treatment and Diagnosis

(DCTD), informed the Board that the Clinical Trials Implementation Committee report would address many of the Clinical Trials Program Review Group (CTPRG). The Board was asked to respond to the plan as outlined with approval to proceed with implementation or suggestions for further modification.

Background. The Co-Chair, Dr. John Glick, Professor of Medicine and Director, University of Pennsylvania Cancer Center, reviewed the committee's makeup, charge, and the process. Dr. Glick stated that in addition to responding to CTPRG recommendations, the BSA and NCAB challenged the CTIC to address the optimal structure, function, and funding of the cooperative group program. Based on the CTPRG report, the major topics were science, development, peer review, trial simplification, consensus development, streamlining procedures, informatics, information dissemination, broadening access, participation reimbursement, partnership formation, training, and human subjects' protection. The process involved developing a common functional vision for the clinical trials system, responding to each CTPRG recommendation, and reviewing, discussing, and modifying models for changes to the current system.

Ongoing and Planned Initiatives. Dr. Michael Christian, Co-Chair and Associate Director, Cancer Therapy Evaluation Program (CTEP), DCTD, gave an overview of the NCI's ongoing and planned activities related to five of the major focus topics: Better Science, Efficiency and Streamlining, Partnerships and Industry Interactions, Human Subjects' Protection, and Training Programs. The CTIC endorsed holding an information technology conference and recommended that the NCI place a high priority on its efforts to pilot a national Institutional Review Board (IRB), take an active role in interacting with IRBs, and enlist the assistance of advocacy groups in this effort.

In discussion and in response to questions, the following points were made:

- The development of criteria for approval of chemoprevention drugs should be an agenda item in NCI discussions with the Food and Drug Administration (FDA).
- Currently, the responsibility for compliance with all human

subject recommendations rests with the cooperative group operations offices, the CTEP Clinical Trials Monitoring Branch, and the NIH Office of Protection from Research Risks (OPRR).

- A set of rules or approaches is needed to deal with industry/academia research interrelationships in the areas of data, analysis, and publishing rights.

Clinical Trials Cooperative Group Program. Dr. Glick reviewed the history of the clinical trials cooperative group program and described the program as it is currently configured, including the strengths, weaknesses, and the CTIC's vision for the program's future. The need to retain many strengths of the program was emphasized. Observed weaknesses were related to limited scientific input, slow or inadequate accrual, underemphasis of innovative pilot trials, adequate reimbursement for time and effort, limited "real time" external review, administrative load, and limited peer review of individual protocols.

CTIC's Vision, Pilots, and Plans. The elements comprising CTIC's vision of a future clinical trials framework towards promoting better science would involve a broader pool of idea generators, competition among idea generators, disease-specific concept review committees, state-of-the-science meetings, and enhanced peer review. Efficiency and streamlining of protocol development, protocol activation, and conduct of the trials would be implemented through uniform informatics and Clinical Trials Support Units (CTSUs). Accrual would be increased and access would be broadened through open menu/cross group registration to make clinical trials a viable option for all patients and to involve new physicians. The CTIC also envisioned adequate compensation per accrual reimbursement, the availability of scientific leadership funds, and restoration of cooperative group funding to fully recommended levels.

Using a schematic of the envisioned framework for clinical trials, Dr. Christian stated that key components of the envisioned system were state-of-the-science meetings, idea generator, disease-specific concept review committees for real-time scientific review of Phase III trials, CTSUs to consolidate many of the administrative and duplicative functions, and the network of cooperative group and nongroup investigators enrolling patients on NCI-sponsored

clinical trials. As a replacement for the CTEP/group member strategy meetings, state-of-the-science meetings would be national forums to identify new research opportunities or gaps in the NCI research portfolio. Proposed pilots in this area would be meetings for genitourinary (GU) and lung cancers organized by CTEP and gastrointestinal (GI) cancers and leukemia meetings organized by the cooperative group chairs.

The process for 1) accepting, analyzing, reviewing, and approving concepts; 2) developing and administering protocols; 3) ascertaining concept review committee composition; and 4) defining NCI staff participation was described. Members were informed that the CTIC went beyond CTPRG recommendations regarding concept review and envisioned a more broadly constituted review committee, which is a key feature of the plan. To ensure that the future system will be better than the current system, the CTIC proposed possible metrics for evaluation of the pilot projects. The CTIC also recommended that an expert consultant be hired to establish a formal evaluation plan.

Approximately three CTSUs are envisioned to replace the current 12 administrative structures for clinical trials support. This would reduce duplication, promote the use of uniform procedures, and consolidate administrative functions, leaving the groups to concentrate on science and maintain smaller operations and data management offices. Possible metrics were proposed for the evaluation of clinical trial administration by the CTSUs. The proposed network of physician participants would include both cooperative group members and nongroup investigators who would have access to the entire menu of approved NCI-sponsored Phase III trials and who would be reimbursed for costs based on patient accrual and data quality. Recommendations for a more effective peer review included real-time review of individual projects, streamlined application and review process, and revision of review criteria to reflect enhanced objectives of the cooperative group program.

In responding to the request for guidance in determining the optimal structure, function, and funding for the cooperative group, including the number and size of the groups, the CTIC believed that the question had been answered in the process of defining the components of a clinical trials system that (1) enhances science and competition, (2) approves only the best ideas, (3) strengthens peer

review, and (4) facilitates flexible redirection of funds. The proposed changes would optimize investment in the best science and allow the system to self-correct without arbitrary downsizing.

The program review and implementation deliberations have been the impetus for much interaction and discussion in the research community. Notably, the cooperative group chairs met four times to discuss issues related to improving their own clinical trials operations. The group chairs proposed another model for pilot testing that featured blocks of activities to be conducted in a clinical trials system similar to those in the CTIC plan, i.e., regulatory, information, science, and technology. They proposed that strategy meetings be organized to reach consensus about Phase III trials, intergroup committees be convened as appropriate, and that group resources would be committed toward the rapid completion of the trials. Pilot disease sites would be GI cancers and leukemias.

The CTEP proposes to evaluate the performance of the Phase III consensus development components of both the CTICs and cooperative group chairs' proposals in two sets of pilots. Measures to support this activity would include the collaborative development of the CTSU, supplemental funding for strategy and intergroup meetings and for leadership of intergroup trials in GI, leukemia, and other sites, and collaborative development of common data elements and case report forms. In summary, the approach to implementing the CTIC plan is a series of pilots together with the prospective development of evaluative tools to ensure that the new mechanisms are better and promote more effective partnerships among the many constituencies. The BSA would be actively involved in the evaluation.

In subsequent discussion and in response to questions, the following points were made:

- The CTSUs as envisioned would be a system primarily for large Phase III trials. There would continue to be a need for smaller, more streamlined operations offices in each cooperative group to handle developmental research and industry studies.
- Disease-specific review committees would be piloted in

only two diseases, but will probably be needed in most of the major diseases if the review committees are an effective mechanism. A concern was expressed that the prioritization among several different groups would be more difficult than if a more centralized group were doing all of the evaluation. Another member noted the need for a clarifying discussion related to the disease-specific concept review committee as proposed and the role of the new Clinical Oncology Special Emphasis Panel.

- Efforts should be made to avoid competing Phase III studies within cooperative groups because of the risk of an inherent selection bias if an institution has several Phase III studies with different approaches going on concurrently, as well as the risk of not completing less attractive studies as new ones are acquired. Staff responded that institutions already have multiple ongoing trials, and that bias is inherent in the current system but large-scale studies with internal stratification and prospective randomization should be able to address that; moreover, there are disincentives to activating too many trials within a single institution.
- Developmental studies that are funded through the Rapid Access to Intervention Development (RAID) program, until proof of principle is established, could be developed in the early clinical trials and Phase II components of the CTIC plan, but those studies would compete with all other protocols for definitive Phase III trials.
- The clinical trials cooperative groups have had an enormous impact on raising the general community standard of oncologic care, and that is a valuable function.
- The CTIC plan does not differ much from actual practice in that many first-line studies were intergroup studies, and all resulted in publications in the last year. The proposal to provide study coordinators resources is important and the concept for conducting pilots is good.
- To be able to judge the efficacy of one pilot versus another, the per case reimbursement rate must be equalized across the entire system, including Community Clinical Oncology

Program (CCOP) participants.

Summary Comments: Members were reminded that, as the implementation process began, three preeminent concerns were the scientific content of the clinical trials program, access to it by both physicians and patients, and functionality of the system. The deliberations of the CTIC have focused on redesigning aspects of the present program to provide those characteristics. Initiatives already in place are the RAID program and restructuring of informatics systems that serve the clinical trials program. To the maximum extent possible, all constituencies have been involved. The vision for the CTSUs was that they would create a user-friendly interface between the entire U.S. patient community or all physicians interested in participating and the clinical trials program. Proposed changes to the concept review process were viewed as the replacement of an NCI staff role with a largely peer-review process. The state-of-the-science meetings were seen by the CTIC as an attempt to make the process more open and more sensitive to the present state-of-science in particular areas.

In the discussion, the following points were made:

- The CTIC proposal recognizes the importance of the present clinical trials system in the evaluation of new therapeutics and has proposed changes, such as the national IRB, that can boost accrual rates by lowering barriers. The possibility that the proposed changes to the peer-review process could create another bureaucracy is a concern and should be monitored.
- Two important marketing strategies will include communicating reliable information about the evolving program as improvements become manifest ensuring that the system is adequately funded to address some of the imputed structural problems. At the same time, the NCI is developing a public education program for clinical research and for clinical trials, which is expected to be ready in the next few months.
- In the evolutionary process that has been proposed, BSA's immediate involvement could take the form of a subcommittee to work with CTEP on an ongoing basis or a

progress report in 6 months. Three issues that should be revisited in 6 months are evaluation of the pilots, the timeline for implementation of the funding proposals, and the peer-review process. The Clinical Trials Implementation Group report should be developed into a brief and polished format before it is distributed to the health care community.

- When queried about the proposed merger of the four pediatric clinical cooperative groups raised a question related to the plans for the review process, staff responded that the pediatric merger was another pilot in the sense that it builds on many recommendations of the CTPRG and CTIC reports. Some of the redundant administrative functions would be eliminated, the clinical trials menu would be opened, and a more unified approach would be employed for the integration of early clinical trials into definitive Phase III studies. One anticipated result is an expanded research portfolio that includes innovative, population-based studies, such as national registries and epidemiology studies in childhood cancer. The proposal will be discussed in fall meetings, and the assistance of the CTEP Clinical Investigations Branch will be sought. The NCI Grants Review Branch and the CSR would be consulted for advice on how the issue of review could be addressed.

Motion: A motion to approve the Clinical Trials Implementation Group plan with the caveat that a an interim report, written or oral, on the process and on how progress would be evaluated, should be presented to the Board in 6 months and that a Board decision regarding the timeline for an outcomes review will be given at a later date was approved with 20 for and 1 against.

DEVELOPMENTAL THERAPEUTICS PROGRAM REVIEW GROUP (DTPRG) REPORT - DR. ROBERT WITTES, AND DR. SUSAN B. HORWITZ

Dr. Susan B. Horwitz, Chair, DTPRG, Albert Einstein College of Medicine, presented highlights of the review of NCI's Developmental Therapeutics Program (DTP) and DTPRG recommendations. The charge to the PRG was 1) define the future of the NCI in the discovery and development of new chemicals and

biologicals for the treatment of cancer, and 2) develop a vision blueprint for the future of anticancer drug development. Dr. Horowitz reported that the DTP is primarily an extramural program with a large part of the DTP budget included within the research project grant (RPG) pool and a remaining portion allocated to extramural project contracts. Approximately one-half of the contracts supports extramural research conducted in-house at NCI's Frederick Cancer Research and Development Center (FCRDC) and the other half supports non-FCRDC extramural contracts. To enhance the ability to discover new and useful antitumor drugs during the next decade, Dr. Horowitz reported that the DTPRG recommended the following recommendations:

- **Allocation of Funds and Role of the Extramural and Intramural Programs.** All in-house DTP activities should be limited to 15 percent of the total budget. The DTP should assume a leadership role in informatics to facilitate the development of cancer therapeutics. The DTP also should expand its current operations in the area of coordination and dissemination of information about resources that are available to cancer investigators working in the area of drug development. Extramural funding, which should constitute about 85 percent of the budget, should be used to support the cooperative groups, such as the National Cooperative Drug Discovery Groups and National Cooperative Natural Products Discovery Groups, extramural contracts, and Centers of Excellence.
- **Decision Network (DN) Committee.** The DN Committee, which is responsible for prioritizing drugs for clinical development, should be expanded to include representatives of academia and cancer centers as well as NCI staff. A majority of the PRG believed that the DN Committee should review both drugs and biologics. The DTPRG subcommittee on biologics, however, believed that a separate committee with appropriate expertise should continue to analyze and prioritize biologics.
- **Monitoring and Oversight of the DTP Research Portfolio.** A flexible and rapid-response mechanism to deal with changing research objectives and resource requirements that arise on a month-to-month basis is needed. The DTPRG proposed the creation of a committee

of scientists (5 to 8) chosen from among the leadership of DTP, academia, and industry with the authority to evaluate and fund grants or invest contract resources in projects that are submitted to DTP through the extramural program or proposed by in-house DTP personnel. The committee would prioritize the distribution of resources available to DTP and be responsible for the discovery of novel therapeutics and novel drug discovery technologies.

- **Major Recommendations of the DTPRG Subcommittees.** Dr. Horwitz explained that five subcommittees were formed to review the areas of small molecule diversity and screening technology; structural inventory of potential drug targets; animal models; pharmacology, toxicology, and formulation; and biologics. Major recommendations of these groups were to: support a chemical diversity program with the goal of finding small molecules that can manipulate the function of all proteins or processes relevant to cancer; undertake a major interdisciplinary initiative to acquire structural information on cellular targets that are potentially relevant to cancer; reconfigure the NCI program for screening compounds for antitumor activity to ensure responsiveness to changes in science and technology; reduce the current 60 cell-line screen to 3 cell lines focused on the identification of lead compounds based on cell proliferation inhibition; establish Centers of Excellence in a variety of scientific areas, for example, pharmacology and toxicology core facilities; and expand the scope of the Biologic Resources Branch by augmenting the categories of biological reagents that are currently being produced and by developing novel technologies and capabilities for the production of recombinant vectors. A series of scientific and administrative programmatic recommendations developed in the five areas were presented.

In discussion, the following points were made:

- DTPRG recommendations regarding the expansion of the Biologic Resources Branch reflect the changes that have taken place in the understanding of molecular immunology and development of new targets and the need to accelerate research in these areas. Moreover, the NCI is recognized as having the expertise and resources needed to translate the

radically new biologic approaches into early proof-of-principle Phase I clinical trials that are not available in the industry.

- A point-by-point response to the DTPRG recommendations similar to that received in response to the CCPRG report was requested. The plan would include projected costs, a timeline, and strategy for implementing the recommendations. An indication of how to integrate elements in this report with the prevention drug development program should be included. Staff indicated that a plan will be developed and that the NCI will ask the BSA and DTPRG members for assistance. The response should be ready for presentation at the March 1999 BSA meeting.

Motion: A motion was made to accept the Developmental Therapeutics Program (DTP) Review Group Report and the request that NCI submit a point-by-point response to the BSA at its March 1999 meeting on the feasibility of implementation of the report recommendations and cost projections. The motion was seconded and unanimously approved.

Adjournment: The 9th and special meeting of the Board of Scientific Advisors was adjourned at 4:22 p.m. on Wednesday, 23 September 1998.