

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE**

47th Meeting

BOARD OF SCIENTIFIC ADVISORS

Minutes of Meeting

**November 1, 2010
Building 31C, Conference Room 10
Bethesda, Maryland**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE**

BOARD OF SCIENTIFIC ADVISORS

**MINUTES OF MEETING
November 1, 2010**

The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 47th meeting on Monday, 1 November 2010, at 9:00 a.m. in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Richard L. Schilsky, Professor of Medicine, Section of Hematology and Oncology, Biological Sciences Division, University of Chicago Pritzker School of Medicine, presided as Chair. The meeting was open to the public from 9:00 a.m. until 3:37 p.m. on 1 November for the NCI Director's report; a report on NCI Congressional relations; a status report on the HMO Cancer Research Network; establishment of a BSA Working Group; the annual requests for applications (RFAs) concept report; consideration of request for proposals (RFP), RFA, and Cooperative Agreements (Coop. Agr.) reissuance concepts presented by NCI program staff; and a report on the overall process of proposing and evaluating RFAs.

BSA Board Members Present:

Dr. Richard L. Schilsky (Chair)
Dr. Paul M. Allen
Dr. Christine Ambrosone
Dr. Andrea Califano
Dr. Michael A. Caligiuri
Dr. Arul M. Chinnaiyan
Dr. Curt I. Civin
Dr. Robert B. Diasio
Dr. Jeffrey A. Drebin
Dr. Betty R. Ferrell
Dr. Kathleen M. Foley
Dr. Sanjiv S. Gambhir
Dr. Todd R. Golub
Dr. Joe W. Gray
Dr. Mary J. C. Hendrix
Dr. Marc A. Kastner
Dr. Timothy J. Kinsella
Dr. Joshua LaBaer

Mr. Don Listwin
Dr. Christopher J. Logothetis
Dr. James L. Omel
Dr. Edith A. Perez
Dr. Stuart L. Schreiber
Dr. Bruce W. Stillman
Dr. Victor J. Strecher
Dr. Louise C. Strong
Dr. Frank M. Torti
Dr. Jean Y. J. Wang
Dr. Irving L. Weissman
Dr. James K. Willson

Board Members Absent:

Dr. Chi V. Dang
Dr. Ronald Anthony DePinho
Dr. Elena M. Martinez

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

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I. CALL TO ORDER AND OPENING REMARKS - DR. RICHARD L. SCHILSKY

Dr. Richard L. Schilsky called to order the 47th regular meeting of the BSA and welcomed current and new members of the Board, NIH and NCI staff, guests, and members of the public. Dr. Schilsky reminded Board members of the conflict-of-interest guidelines and confidentiality requirements. Members of the public were invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), in writing and within 10 days, comments regarding items discussed during the meeting.

II. CONSIDERATION OF THE 28 JUNE 2010 MEETING MINUTES - DR. RICHARD L. SCHILSKY

Motion: The minutes of the 28 June 2010 meeting were approved unanimously.

III. REPORT OF THE DIRECTOR, NCI - DR. HAROLD VARMUS

Dr. Harold Varmus, Director, NCI, welcomed members and provided information about the NCI's budget for fiscal years (FY) 2011 and 2012, changes of scientific emphasis within the NCI and across the NIH, and discussed ways to accelerate NCI's advances in scientific discovery and cancer research. Dr. Varmus told members that the current economic situation means that NIH budgets will have less flexibility. He stated that all of NCI's work should be conducted at a high level of excellence, and asked the Board for input regarding areas to improve and/or better ways to spend funds.

Budget: Dr. Varmus informed members that the Institute continues to operate under a continuing resolution at the FY 2010 appropriations level. Members were told that the NCI is currently managing its budget through a conservative approach, such as paying continuing noncompetitive awards at 90 percent of full value. He indicated that he does not consider the funding payline as an absolute number and plans

to have flexibility in terms of funding grants, based on a combination of impact/priority scores and a project's novelty and ability to advance scientific discovery. Members were told that the NCI has received an increase in the number of applications during the past year, partly because many unsuccessful American Recovery and Reinvestment Act (ARRA) applications are being submitted as individual investigator (R01) applications. Dr. Varmus invited comments from the Board on ways to re-allocate resources in the current budget environment. He noted that, as requested, ARRA monies and appropriated funds have been kept separate in the accounting process. Thus, there is no expectation that projects supported or dramatically supplemented by ARRA monies will be continued.

Dr. Varmus stated that the NCI conducted a 5 percent reduction exercise for the FY 2012 budget per an NIH-wide request by the Office of Management and Budget (OMB). In tandem with this exercise, Dr. Francis Collins, NIH Director, conducted a competitive exercise among the Institutes and Centers (ICs), inviting them to indicate both reductions and their plans for advancing their missions. Members were told that in the next month the NCI will prepare its FY 2012 bypass budget with a narrative report that describes NCI accomplishments and recent successes as well as immediate prospects for the next year and long-range goals; he encouraged members to share ideas for the report.

Institutional Changes: Dr. Varmus told the Board that changes to the NCI organization included Dr. Douglas R. Lowy as the newly appointed Deputy Director. Additionally, the NCI is recruiting for several positions, i.e., Deputy Directors for clinical and translational research and for administration; Directors for the new centers on cancer genomics and global health; and Presidential appointments to the National Cancer Advisory Board (NCAB). Several ongoing activities include the: 1) NCAB *Ad hoc* Working Group To Create a Strategic Scientific Vision for the National Cancer Program and Review of the National Cancer Institute is preparing a report to advise the Director; 2) NCI's response to the Institute of Medicine's (IOM) report on the clinical trials and cooperative groups, which includes recommendations for consolidation and reorganization of the groups; and, 3) NIH-wide Cures Acceleration Network (CAN) initiative, which was included in the Health Reform Act and authorizes \$50 million (M) of existing funds in FY 2011 to CAN and up to \$500M over time. Intense discussions about CAN are underway among the NIH and IC leadership.

Additionally, the NIH Scientific Management and Review Board (SMRB) has recommended new ways to fund the NIH Mark O. Hatfield Clinical Research Center (CRC), including that the CRC's budget be incorporated within the Office of the Director of NIH. The SMRB also is examining how therapeutic development and translational research are organized, which interdigitates with the CAN initiative. These SMRB activities are among the reasons why an NCI Deputy Director focused on translational research activities would be helpful. The SMRB also voted favorably to create a new Institute devoted to addiction and substance abuse while closing the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism. Dr. Collins, NIH Director, and Hon. Kathleen Sibelius, Health and Human Services (HHS) Secretary, need to respond to the recommendation, before Congress has the opportunity to take action. A portion of NCI's portfolio, particularly related to tobacco, may be affected.

Intramural Research Program: Dr. Varmus informed members that he was impressed by the organization of the NCI's Center for Cancer Research (CCR) and the use of the Stadtman Award Program as a means to recruit young investigators to the NIH. The Intramural Research Program also has made appropriate changes in response to critiques from the Board of Scientific Counselors (BSC), which recommended increased recruitment of new investigators and budget reductions for some existing investigators. Because of a longstanding difficulty in recruiting clinical investigators at the middle and higher levels, NCI leadership is emphasizing recruitment of researchers at a more junior level through a new program called the Lasker Scholars Program in conjunction with the Lasker Foundation. This program provides the opportunity to work at the CRC, and offers a tenure-track position or an additional 2 years of support if the investigator chooses to return to extramural research.

NCI Organizational Changes: Dr. Varmus discussed the establishment of two new Centers that will focus on cancer genomics and global health. He noted that the Center for Cancer Genomics will enfold The Cancer Genome Atlas (TCGA) project and other genome initiatives under one group at a time when

genomics is becoming central to cancer research. A search is underway for a Director who can bring a deep perspective on the nature of oncology and the role of genomics in cancer research, as well as the managerial ability to operate many genomics projects. The Director will need to address profound changes in how oncology and genomics is conceptualized, such as: how the cancer genomics community can better educate physicians about changes in oncology; how the practice of oncology is regulated and patients are assigned to therapeutic regimens based on genomic information; and certification of laboratories that perform these unique tests.

The Center for Global Health is intended to provide an opportunity to improve health and life expectancies at a time when the burden of cancer has shifted dramatically, .i.e., more than two-thirds of cancer deaths occur in poor countries. The NCI can play a significant global role in preventing cancers through vaccines against hepatitis B and human papilloma viruses and promoting tobacco control. Dr. Varmus indicated that the Center's Director will need to examine NCI's existing portfolio and consider how the Institute can build upon cancer control efforts occurring elsewhere in the government, including through the President's Emergency Plan for Acquired Immunodeficiency Syndrome (AIDS) Relief (PEPFAR), the AIDS program, and activities of the U.S. Agency for International Development (USAID) and other agencies. He noted that this will require an understanding of how global health research is conducted, how to work with finance ministers in other countries, and how to take advantage of other efforts that are already underway in developing countries. Members were invited to submit recommendations for the Deputy Director of Clinical and Translational Research and Directors of the Center for Genomics and the Center of Global Health.

Provocative Questions: Dr. Varmus expressed his interest in addressing the deep biological questions that will change the way cancer is approached. He informed members that Drs. Lowy, Tyler Jacks, and Ed Harlow are assisting him with the "Provocative Questions Exercise" (initially entitled "The Big Questions Exercise"), which raises questions that could lead to a deeper understanding of cancer and questions that are amenable to solutions with new technologies. During an initial meeting on 9 October 2010, a decision was made to engage a broader group in discussions through a Web site and future meetings over the coming months. Specific questions that were developed at the October meeting include: Why is chemotherapy effective in treating and even curing some cancers (e.g., cisplatin cures testicular cancer)? What is the nature of the association between obesity and cancer, given that obesity is a predisposing factor? Is it a reversible relationship? Some of these questions may provide topics for future RFAs and RFPs, and the NCI may form a study section to review applications that address three or four of these questions.

BSA Working Group: Dr. Varmus stated that some existing programs are being reviewed to consider ways to conserve resources and improve approaches and efficiency. One example is the Cancer Biomedical Informatics Grid (caBIG®), which will be discussed by a BSA Working Group tomorrow, pending approval of the working group by the BSA. Dr. Varmus invited members to submit topics that might warrant greater scrutiny.

In the discussion, the following points were made:

- ▶ Collaborations with other organizations and entities will be accomplished through a combination of informal interactions and formal structures, particularly in situations requiring co-funding. Cross-agency dialogue is important because many of the issues facing the NCI are jurisdictional, political, or revolve around leveraging funding across agencies.
- ▶ The NCI and the National Human Genome Research Institute (NHGRI) have planned a retreat to discuss the progress of the TCGA.
- ▶ A role for the U.S. extramural cancer community in planning and participating in global health and cancer should be identified by the new Director of the NCI Center for Global Health.

NCI is encouraged to consider mechanisms to support large collaborative applications reviewed by NCI peer review committees. Members were informed that the NCI SPL committee is discussing the issue of peer review as well as how to promote inter-institutional, collaborative awards.

Dialogue with the FDA and industry should be encouraged to discuss novel approaches to combination therapies as well as biological, genetic, and diagnostic tools.

Members expressed support in helping the NCI review its current portfolio to determine programs to eliminate or cut back to provide funding for new initiatives.

IV. NCI/CONGRESSIONAL RELATIONS - MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), informed members that the President's Budget (PB) for FY 2011 was announced on 1 February, with \$32.09B for the NIH and \$5.26B for the NCI. Ms. Erickson provided an update on NCI testimonies, upcoming hearings, and legislation of interest, including 21st Century Cancer Access to Life-Saving Early Detection, Research and Treatment (ALERT) Act (HR6224) and Cancer Centers Assistance for Renovations and Expansion Act (HR5861).

In the discussion, the following point was made:

The NCI and cancer community at large have a mission to educate new and returning members of Congress about the importance of cancer research to promote public health.

V. STATUS REPORT: HMO CANCER RESEARCH NETWORK - DRs. RACHEL BALLARD-BARBASH, MARK HORN BROOK, REBECCA SILLIMAN, CHYKE DOUBENI, AND REBECCA SMITH-BINDMAN

Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences (DCCPS), introduced the presentation on the HMO Cancer Research Network (CRN). Dr. Croyle briefly described plans by NIH for a Commons Fund initiative for questions common across institutes based on the CRN. He then introduced the speakers: Drs. Rachel Ballard-Barbash, Associate Director, Applied Research Program, DCCPS; Mark Hornbrook, Chief Scientist, The Center for Health Research, Northwest/Hawaii/Southeast, Kaiser Permanente; Rebecca Silliman, Professor, Departments of Medicine and Epidemiology, Boston University Schools of Medicine and Public Health; Chyke Doubeni, Assistant Professor, Department of Family Medicine and Community Health, University of Massachusetts Medical School; and, Rebecca Smith-Bindman, Professor, Departments of Radiology, Epidemiology and Biostatistics, and Obstetrics, Gynecology, and Reproductive Medicine, University of California, San Francisco.

Introduction – Dr. Rachel Ballard-Barbash

Dr. Ballard-Barbash explained that the CRN started in 1999 and was most recently funded in 2007, through a U19 Cooperative Agreement/Research Network Grant. The network members are 14 research organizations affiliated with large health maintenance organizations (HMOs) covering nearly 11 million individuals. CRN research spans the cancer control continuum, including prevention, screening and early detection, tumor biology and treatment, survivorship, and end-of-life. Research themes include health services research, epidemiology, dissemination and implementation of research findings, and health insurance benefit designs and patterns of care. Recently, emphases on cancer communications, psychosocial factors, and quality of life were added to the program. The network has developed a virtual data warehouse (VDW), using a federated data system model, to combine data from all of the HMOs and research projects. The CRN provides unique opportunities to document changes in patterns of care in response to new research findings. Since 2006, CRN and affiliated investigators have received competitive funding for 17 NIH grants and 8 projects funded by other agencies and have published more than 100 scientific papers, most in leading journals in their fields. CRN also has a Pilot Research Program and a Scholars Development Program, both of which provide research opportunities for junior

investigators. The Scholars program provides hands-on mentorship and networking opportunities and has led to funded R-level, Grand Opportunity, and Challenge grants, training awards, and manuscripts.

CRN Informatics Research and Development – Dr. Mark Hornbrook

Dr. Hornbrook explained that key informatics resources of the CRN include the capacity to rapidly summarize clinical data to assess study feasibility and inform study design and logistics, as well as the ability to link census and other geospatial information with HMO clinical data. CRN is on the cutting edge of assessing the usefulness of emerging informatics tools, such as natural language processing and distributed research networks, and of implementing oncology electronic medical record (EMR) systems and adapting them for research purposes. The CRN Cancer Counter Query Tool uses tumor registry data to produce Health Insurance Portability and Accountability Act (HIPAA)-compliant tabulations, providing information about 12 cancer-relevant variables; it supports data queries preparatory to research and can help investigators decide whether a study is feasible. Another tool used by the CRN, a commercial data query tool called i2b2, enables investigators to access data files without the assistance of a programmer or statistical analyst. Natural language processing is a high-priority tool because it enables extraction of coded data from free text EMRs, such as data on smoking behavior. Dr. Hornbrook concluded by informing members of several of CRN's research resources key strengths, including defined populations covered by ambulatory EMR systems, with inpatient EMRs soon to be added; access to physician-patient communications on secure Web portals; and tools for accessing and analyzing HIPAA-compliant patient-level health information not available outside of health plans. All CRN partners will participate in FDA's Mini-Sentinel Drug Safety Surveillance program, which will enable them to apply safety hypothesis testing models to cancer therapeutics. Additionally, the CRN is developing biospecimen repositories that can be linked to EMRs.

Breast Cancer Research in the CRN – Dr. Rebecca Silliman

Dr. Silliman informed the Board that the CRN's breast cancer research vision is to use the CRN population, data resources, and access to biological specimens to address key breast cancer research questions throughout the continuum from risk prediction to survivorship. Recent areas of emphasis include diffusion and comparative effectiveness of new technologies, the role of biomarkers, and quality of care. Key studies using a historical cohort design have focused on prophylactic mastectomy (PM), including contralateral PM after a breast cancer diagnosis and bilateral PM in those at elevated risk; the use of biomarkers to predict ductal carcinoma in situ (DCIS) recurrence; and investigations of outcomes in older women. One such study demonstrated that breast conserving surgery (BCS) alone had a poorer outcome than mastectomy or BCS with radiation. Another study demonstrated that nearly 50 percent of women receiving tamoxifen discontinued their medication before completing 5 years of therapy, confirming other evidence that adherence to oral therapies is a challenge in cancer care. Dr. Silliman informed members that a study of the effectiveness of surveillance mammography found that mammography was protective in relation to breast cancer mortality and that the effect grew stronger with each additional surveillance mammogram. Future directions for breast cancer research in the CRN include using recently developed informatics tools to confirm past findings in more contemporary patient samples, as well as studies designed to inform and optimize the care of older breast cancer patients.

A Career in Cancer Research in the HMO CRN – Dr. Chyke Doubeni

Dr. Doubeni described his personal experience as a physician and stated that he found opportunities for research in the CRN initially through a K01 award research supplement for under-represented minorities, followed by a pilot project in the CRN Scholars Program, which led to two independent research awards. He stated that one of his projects investigated patterns and predictors of mammography utilization among breast cancer survivors and demonstrated that those who visited gynecologists or primary care physicians had a higher likelihood of having mammograms. Another project demonstrated that racial/ethnic disparities were associated with differences in the use of medical services for colorectal cancer-specific deaths in insured populations. Dr. Doubeni informed members that one of his current projects involves establishing a center for cancer screening comparative effectiveness research (CER) in the CRN; the other

project is investigating the effectiveness of screening colonoscopy relative to sigmoidoscopy in reducing deaths from colon cancer, particularly for cancers in the right colon. Dr. Doubeni emphasized the value of the CRN as an environment for career development that provides rich resources, relationships, and mentorships for the next generation of investigators.

UCSF Collaborative Study: Medical Radiation and Cancer Risk – Dr. Rebecca Smith-Bindman

Dr. Smith-Bindman described a study she led at Group Health Cooperative, one of the CRN sites, which demonstrated a 10-20 percent annual increase in imaging using newer technologies (computed tomography [CT], magnetic resonance imaging, and positron emission tomography). She noted that this finding and others have prompted safety concerns, especially for CT, because of variability in radiation doses across institutions and substantial evidence that CT is carcinogenic. Members were told that a pilot study of CT safety with several CRN sites showed that the costs of imaging across the CRN have tripled over 15 years and that there are dramatic and unexplained differences both in the use of imaging and in the radiation dose from the same type of imaging across different settings. CER studies to identify the optimal use of imaging and efforts to standardize doses to appropriate levels clearly are needed. Future planned studies will take advantage of the CRN's ability to retrieve imaging studies over the past 15 years and follow enrollees for many years to assess for cancer. A proposed study, Appropriate Radiology Imaging for Safety and Effectiveness (ARISE), includes 70 million person years of follow up, including 150,000 cancers, and may provide definitive answers to a broad range of questions and rapid dissemination of research results to improve care. Dr. Smith-Bindman told members that CRN is the only organization in the United States where such a study is feasible.

In the discussion, the following points were made:

Although the studies described were primarily observational, the CRN has the capacity to do intervention studies as well.

The CRN has the capacity to collect biospecimens and several CRN centers are building biobanks.

Full integration of databases from the HMOs creating a true network would be valuable, including integration of costs in the analysis and providing greater dissemination of research findings.

Although good data now exist on the adverse impact of undertreatment in older women, those data have not been translated into changes in care. The CRN is ideally positioned for future research to design and test interventions to improve care for older women with breast cancer.

The CRN data is a publicly available resource for very specific research questions. Researchers must submit a proposal, which is reviewed by CRN and an Institutional Review Board (IRB).

Collaboration with CRN investigators often is needed for optimal use of the data.

VI. ANNUAL RFA CONCEPT REPORT - DRS. RICHARD L. SCHILSKY AND PAULETTE S. GRAY

Dr. Gray presented the RFA and research and development (R&D) RFP concepts annual report. She noted that the report includes concept data from 1996 through June 2010. She noted that information is reported by the date the concept was presented to the Board and by the Division in which the concept originated. Another section provides a history of RFP review and outcomes. Also included in the report are: 1) graphs and pie charts displaying data for RFA grant funding and overall NCI grant funding, BSA-approved RFA concept set-asides by Division, RFA allocation by concept area, and total NCI grant and RFA funding by concept area as a percentage of total NCI grants; 2) a listing of funded grants; and 3) abstracts of the funded grants in hardcopy and CD-ROM formats. Dr. Gray informed members that the report has been generated annually since the initial BSA request in 1999 to provide background information relevant to the concept. The current report was revised this year to reflect the preferences stated by the Board in 2009. Additionally, future reports will be provided to the Board in PDF and/or

Excel format via the BSA Web site and members will receive passwords for the protected section of the BSA Web site.

In the discussion, the following points were made:

Consideration should be given to incorporating, in Excel format, data from the annual RFA Concept Report on the members-only section of the BSA Website. A comprehensive chart that portrays the NCI's full portfolio of allocations across the years, rather than by individual year should be provided.

Members expressed interest in seeing how the budget is disbursed through trans-NCI programs, such as caBIG®. This would aid members and the BSA Working Group in better understand the larger picture.

VII. ESTABLISH BSA WORKING GROUP - DR. RICHARD L. SCHILSKY

Dr. Schilsky informed members of a proposal to establish a Working Group composed largely of members of the Board to assess the current status of the Cancer Biomedical Informatics Grid (caBIG®). Dr. Varmus said that the bioinformatics grid serves useful functions but faces many information technology challenges, such as the use of cloud computing as opposed to computing behind firewalls. Members were told that the Working Group's charge would be to examine the original vision and actual functions of caBIG®, including conducting interviews of information technology (IT) developers and software users from the broader cancer community, particularly institutions where caBIG® is playing a role. The Working Group would assess caBIG®'s current and future utility and whether this is being done in the best possible way. Dr. Varmus said that he would look forward to receiving the recommendations about caBIG® in early 2011 if the Working Group is established. Dr. Schilsky said that the proposed Working Group roster includes Board members Drs. Andrea Califano (Chair), Arul Chinnaiyan, Sam Gambhir, and Jean Wang, as well as Drs. Geoffrey Duyk, Tim Hubbard, David Lipman, and Lincoln Stein. The Executive Secretary is Dr. Olivia Bartlett.

In the discussion, the following point was made:

Representatives of industry should be included in the BSA *ad hoc* caBIG® Working Group activities, but their involvement should be integrated to prevent delays in completing the charge in a timely fashion.

Motion: A motion to establish a BSA *ad hoc* caBIG® Working Group was approved unanimously.

VIII. RFP/RFA/COOPERATIVE AGREEMENT CONCEPTS - PRESENTED BY NCI PROGRAM STAFF

**Division of Cancer Prevention
Cancer Prevention Agent Development Program: Preclinical Chemopreventive Agent
Development Research Program (RFP)**

Dr. Peter Greenwald, Director, Division of Cancer Prevention (DCP), introduced the concept for the renewal of a contract program to identify, develop, and quantify drugs for chemoprevention clinical trials, which is part of DCP's overall chemoprevention drug development program (CADP). Dr. Greenwald stated that a recent external review of the CADP recognized that the program addresses an important unmet need and recommended areas where the program could expand and be improved, including discovery, development, and the prioritization process. He noted that modifications have been made to the program to streamline and target the development of promising new chemopreventive agents and to expedite their delivery to the high-risk public. He introduced Dr. Vernon Steele, Acting Group Leader, Chemoprevention Agent Development Research Group, who presented additional information requested by the BSA concept review Subcommittee.

Dr. Steele explained that the primary purpose of the preclinical effort is to develop drugs and qualify them for clinical trials. He noted that the process involves three steps: 1) *in vitro* and *in vivo* screening; 2) animal efficacy testing; and, 3) preclinical pharmacology and toxicology testing. Additionally, it is very difficult for potential chemopreventive agents to be successful through this pipeline, because their toxicity must be minimal since they would be given to essentially healthy people.

Members were told that agents can enter the pipeline at different points depending upon previous research. The work is performed by 12 prime contractors, who have more than 70 principal investigators at more than 40 academic and research institutions. Many agents currently are at different stages in the preclinical development pipeline or are now in Phase I or Phase II clinical trials. One successful example involves a combination of non-steroidal anti-inflammatory drugs (NSAIDs) with difluoromethylornithine (DFMO), which has progressed to a phase II/ III trial of sulindac and DFMO. Dr. Steele also showed other examples of work in progress, including research on Tarceva[®] in a mammary cancer model, where efforts are being made to develop a dosing schedule that minimizes side effects; investigations of the ability of chemopreventive agents to prevent cigarette smoke-induced changes in microRNA; and research on immunoprevention using a combination of Targretin[®] and a vaccine.

Dr. Steele concluded that in the past 6 years, the CADP has led to 20 new Investigational New Drug applications (INDs), 34 new collaborative drug development agreements, and 250 published papers. A total of 200 new agents were screened, of which 67 advanced to efficacy testing and 30 to toxicology/pharmacology testing.

Subcommittee Review. Dr. James Willson, Director, Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, explained that the Subcommittee recognizes that NCI needs to be engaged in chemoprevention, since the pharmaceutical industry has not shown interest and new opportunities exist. Dr. Willson stated that the Subcommittee's original concerns about issues pertaining to toxicology and the FDA IND process were addressed, but uncertainty remains about how the program's advisory teams would be used. He noted that the Subcommittee also expressed concern about adopting new methodologies and whether there would be mechanisms for bringing in scientists who understand new molecular and genomic approaches that might be used to identify potential biomarkers. Additionally, the Subcommittee was informed that the advisory committees include molecular biologists as well as senior scientists who can provide guidance on research strategies. Many of the agents are therapeutic agents and don't need full toxicology studies for an IND. The Subcommittee asked for clarification on intellectual property rights and was informed that when a researcher submits a successful application to the NCI, the technical data are developed by the NCI and intellectual property rights are preserved for both parties. Subcommittee members also raised questions about how the scope of funding for the project influences its results and were told that there is a correlation between the amount of funding and the number of INDs.

The first year cost is estimated at \$16M for 12 awards, with a total cost of \$84.9M for 5 years.

In the discussion, the following points were made:

Members questioned whether NCI needs large contract drug development programs in both DCP and the Division of Cancer Treatment and Diagnosis (DCTD). The development pathway is identical for therapeutic and preventive agents, and the two programs have many features in common and could work synergistically. Program responded that if they were combined, prevention would become a lower priority. In addition, the assays and endpoints of therapy studies are different from those of prevention studies.

Accelerating the development of preventive agents is an important priority. An IND might be filed within 1 to 1.5 years if only a small amount of toxicology is needed, while 4 to 5 years is needed for an agent starting at the beginning of the pathway.

The *in vitro* screens used in this program usually involve primary epithelial cells, mostly human, that are stimulated by carcinogens or other mechanisms to assume a transformed phenotype.

The majority of the CAPD budget is spent on obtaining the required information to have an IND approved; only a small proportion of funds is spent on exploratory work.

The program began working with vaccines during the last 2 years and is collaborating with other NCI groups to develop vaccine methodology and identify areas of overlap.

Members agreed that significant internal oversight over the process of identification and prioritization within this program is needed. To provide the opportunity to restructure the program while maintaining the continuity of the program, members agreed that a reissuance for less than the planned 5 years would be appropriate.

Motion. A motion was made to concur on the Division of Cancer Prevention's (DCP) request for proposal (RFP) entitled "Cancer Prevention Agent Development Program: Preclinical Chemopreventive Agent Development Research Program" but for only 2 years of funding. The motion was approved with 21 yeas, 9 nays, and no abstentions with the provision that the concept would be reviewed by the Board in 2 years for reissuance.

Community Clinical Oncology Program (RFA/Coop. Agr.)
Community Clinical Oncology Program Research Bases (RFA/Coop. Agr.)
Minority-Based Community Clinical Oncology Program (RFA/Coop. Agr.)

Subcommittee Review. Dr. Victor J. Strecher, Professor, Center for Health Communications Research, University of Michigan School of Public Health, expressed the Subcommittee's support for the reissuance of the Community Clinical Oncology Program (CCOP), CCOP Research Bases, and Minority-based CCOP (MB-CCOP), noting that the programs are well established and have effectively linked the NCI and NCI-supported comprehensive cancer centers with the respective communities. The breadth of studies and accrual of patients from community settings have been impressive, the inclusion of prevention and control is a positive aspect, and the recent focus on survivorship issues is timely. The Subcommittee noted that no other known NIH mechanism or center offers a similar program of this scope.

The first year costs are estimated at \$14.3M for 16 CCOP awards, with a total cost of \$74.8M for 3-5 years; \$42.9M for 9 CCOP Research Base awards, with a total cost of \$230.6M for 5 years; and \$3.6M for 6 MB-CCOP awards, with a total cost of \$18.2M for 3-5 years.

In the discussion, the following point was made:

The Board complimented NCI program staff on preparing a well thought out Strategic Plan that provided clear blueprints for the programs' future direction.

Motion. A motion was made to concur on DCP's Request for Applications/Cooperative Agreements (RFAs/Coop. Agrs.) entitled "1) Community Clinical Oncology Program; 2) CCOP Research Bases; and, 3) Minority-based CCOP (MB-CCOP)." The motion was approved unanimously. Re-issuances can be initiated annually for the next 3 years with a BSA status report presented in 2 years.

Division of Cancer Treatment and Diagnosis
Childhood Cancer Survivor Study (RFA/Coop. Agr.)

Dr. Nina Seibel, Cancer Therapy Evaluation Program, NCI, told members that the Childhood Cancer Survivor Study (CCSS) was first funded as a U01 in 1994 and renewed as a U24 in 1999 and 2004. The CCSS is a retrospectively ascertained cohort of long-term pediatric cancer diagnosed survivors between 1970 and 1986. More than 14,000 survivors and 3,700 sibling controls have been recruited. Clinical data on malignancy and treatment were abstracted from medical records, and self-reported data on risk factors

and health as well as psychosocial outcomes were collected. Biospecimens were included starting in 1999 and a second cohort, consisting of children diagnosed between 1987 and 1999, was approved in 2004.

Accomplishments of the CCSS include determining the risk of second malignancy in childhood cancer survivors treated with growth hormone; developing data on the cumulative incidence of chronic health conditions in childhood cancer survivors; clarifying the association between chest radiation therapy and the risk of subsequent breast cancer; and establishing increased risks of congestive heart failure and myocardial infarction in childhood cancer survivors at lower exposures to anthracyclines and radiation therapy than previously recognized. The large size of the CCSS cohort allows more precise estimation of the frequency of both new and previously suspected late effects, and the majority of reports from the CCSS describe new, original findings regarding late effects.

The CCSS provides public access data tables on its Web site. Investigators may request project-specific analytic datasets, of which more than 100 have been provided. Analyses conducted by independent investigators are reviewed by the CCSS biostatistician. Projects using biological specimens must meet scientific priority criteria to justify use of the limited biological material.

Placing the CCSS under the Children's Oncology Group (COG) umbrella would have disadvantages because CCSS enrollees are not restricted to those treated on COG protocols. Also, the CCSS directly abstracts treatment from medical records, rather than classifying patients according to the protocol-specified treatment, and the CCSS focuses on participants who are 10 or more years from diagnosis, whereas the COG focuses on therapy, with 5 to 10 years of follow up. The CCSS has established a highly effective infrastructure, and changes in this structure could compromise the continuity of the project. The CCSS is the first cohort of its type and the largest cohort of childhood cancer survivors in the world.

Subcommittee Review. Dr. Curt Civin, Director, Center for Stem Cell Biology and Regenerative Medicine, Professor of Pediatrics, and Associate Dean for Research, University of Maryland School of Medicine, stated that he was impressed by the quality and importance of the CCSS. Dr. Civin stated that the Subcommittee expressed strong support for the program and recommended incorporating into the language of the RFA the expectation that scientists continue to be at the forefront. The Subcommittee also expressed some reservations about the limited competition aspect of the concept.

The first year cost is estimated at \$4.38M for 1 award, with a total cost of \$21.9M for 5 years.

In the discussion, the following points were made:

The competition is not open because of the established infrastructure in the CCSS and the long term follow-up available on the current cohorts. Outside researchers have access to CCSS data.

Therapeutic practices in childhood cancer continue to evolve and new treatments that may change late effects in survivors should be considered in research design and evaluation.

Motion. A motion was to concur on the Division of Cancer Treatment and Diagnosis' (DCTD) Request for Applications/Cooperative Agreement (RFA/Coop. Agr.) one-time re-issuance concept entitled "Childhood Cancer Survivor Study" was approved with 28 yeas, no nays, and 1 abstention, with the provision that new treatments that may change survivorship effects be considered in research design and annual evaluations.

IX. OVERALL PROCESS OF PROPOSING AND EVALUATING RFAs—DR. DINAH SINGER

Dr. Dinah Singer, Director, Division of Cancer Biology (DCB), explained that RFAs are one of the tools used to support initiatives at the NCI, and that she would first focus on initiatives in general and then on details specific to RFAs. Dr. Singer informed members that initiatives are intended to: 1) facilitate the development of emerging areas of cancer research; 2) respond to resource/infrastructure needs identified

by the research community; and, 3) respond to critical public health needs. The evolution of an initiative involves a sequence of considerations, each leading to a go/no-go decision. First, program staff constantly monitor new scientific developments to identify research opportunities. When it becomes evident that a scientific opportunity is emerging, the NCI often will sponsor a workshop to determine the state of the science and to identify areas where NCI support could make a difference. If there is adequate evidence to warrant developing an NCI initiative, a follow-up workshop or working group may be organized before developing a concept. The majority of workshops organized by DCB do not result in developing new initiatives.

A concept proposal includes sections on the background, scientific rationale, specific goals, and mechanism justification. If a set-aside is planned, the budget must be justified. The concept goes through multiple levels of review before it is issued. The choice of the type of funding announcement is based on the goals of the initiative. Most often, a Program Announcement (PA) (or PAR), requiring no set-aside, is chosen. Concepts are reviewed by the individual divisions and SPL prior to BSA review. Review criteria include the scientific opportunity, need for NCI review and set aside, transdisciplinary interest across divisions, and priority relative to other proposed RFAs. Examples of recent RFAs include the Mouse Models, the Integrated Cancer Biology Program, Trans-disciplinary Research in Energetics and Cancer (TREC), the Early Detection Research Network, and the Cancer Immunotherapy Network.

The percentage of the total discretionary research project grant (RPG) budget that was set aside for RFA funding has increased from about 6 percent to more than 12 percent in the past decade, but a drop is anticipated for FY 2011. Issues to consider pertaining to RFAs include the appropriate criteria for issuing an RFA, whether the current processes for proposing and evaluating RFAs are the correct ones, the fraction of the discretionary RPG budget that should be set aside for RFAs, how to prioritize RFA concepts, and what RFAs should attempt to achieve.

In the discussion, the following points were made:

The success rate for grant applications under RFAs is only slightly higher than for other types of funding, and the entire set-aside is not always used.

Although the involvement of the scientific community in the development of a new initiative can be extremely valuable, NIH policy dictates that individuals who are involved in preparation of an initiative cannot apply for funding under that initiative.

The RFA mechanism should be retained because of concerns regarding CSR reviews.

X. ADJOURNMENT - DR. RICHARD L. SCHILSKY

There being no further business, the 47th regular meeting of the Board of Scientific Advisors was adjourned at 3:37 p.m. on Monday, 1 November 2011.

Date

Richard L. Schilsky, M.D.
Chair, Board of Scientific Advisors

Date

Paulette S. Gray, Ph.D.
Executive Secretary, Board of Scientific Advisors