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

44th Meeting

BOARD OF SCIENTIFIC ADVISORS

Minutes of Meeting

November 2–3, 2009
Building 31C, Conference Room 10
Bethesda, Maryland

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
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BOARD OF SCIENTIFIC ADVISORS

MINUTES OF MEETING
November 2–3, 2009

The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 44th meeting on Monday, 2 November 2009, at 8:00 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 8:00 a.m. until 4:35 p.m. on 2 November for the NCI Director's report; a report on NCI Congressional relations; reports on Comparative Effectiveness Research (CER) and linking Surveillance, Epidemiology and End Results (SEER) and Medicare claims databases to facilitate CER; an update on The Cancer Genome Atlas (TCGA) Program; the BSA Request for Applications (RFA) Annual Concept Report; and consideration of RFAs and requests for proposals (RFPs) reissuance concepts presented by NCI Program staff. The meeting was open to the public from 8:30 a.m. on 3 November until adjournment at 12:00 p.m. for a report on the cancer initiating cell and stem cell biology.

BSA Board Members Present:

Dr. Richard L. Schilsky (Chair)
Dr. Christine Ambrosone
Dr. Andrea Califano
Dr. Michael A. Caligiuri
Dr. Curt I. Civin
Dr. Jeffrey A. Drebin
Dr. Kathleen M. Foley
Dr. Sanjiv S. Gambhir
Dr. Joe W. Gray
Dr. Marc A. Kastner
Dr. Timothy J. Kinsella
Dr. Joshua LaBaer
Mr. Don Listwin
Dr. Christopher J. Logothetis
Dr. Kathleen H. Mooney
Dr. James L. Omel
Dr. Edith A. Perez
Dr. Stuart L. Schreiber
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. Paul M. Allen
Dr. Susan J. Curry
Dr. William S. Dalton
Dr. Chi V. Dang
Dr. Robert B. Diasio
Dr. Todd R. Golub
Dr. James R. Heath
Dr. Mary J. C. Hendrix
Dr. Robert D. Schreiber
Dr. Bruce W. Stillman

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 44th regular meeting of the BSA and welcomed current and new members of the Board, NIH and NCI staff, guests, and members of the public. He 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 22 JUNE 2009 MEETING MINUTES - DR. RICHARD L. SCHILSKY

Motion: The minutes of the 22 June 2009 meeting were approved unanimously.

III. REPORT OF THE DIRECTOR, NCI-DR. JOHN NIEDERHUBER

Dr. John Niederhuber, Director, NCI, welcomed members, including new Board members, and congratulated Dr. Schilsky on his appointment as BSA Chair. Dr. Niederhuber reminded members that the fiscal year (FY)

2009 appropriated budget was $4.968 billion (B), reflecting a 2.9 % increase from FY 2008.

Budget: The NIH Institutes and Centers (ICs) received $7.4 B in funds from the American Recovery and Reinvestment Act (ARRA), of which $1.26 B was allocated to the NCI. The National Center for Research Resources (NCCR) is overseeing $1 B allocated to extramural construction and $300 M to shared instrumentation. Additional allocated funds include: $500 million (M) for NIH construction; $400 M for CER; and $800 M to the NIH Office of the Director (OD). Members were told that the NCI has planned carefully to use ARRA dollars to fund vital science by employing strategies to minimize the out-year effect and particularly by maximizing its ability to generate Congressional enthusiasm about investments in cancer research. A total of 369 research project grants (RPGs) have been funded, extending the NCI FY 2009 payline from the 16th to 25th %ile. The NCI has allocated its ARRA funds to support grants (59%), research and development contracts for the academic community (39%), intramural equipment (< 1%), and support (2%). Dr. Niederhuber informed members that the NIH had funded 140 cancer-related grants totaling $106 M, including: 27 CER awards; 77 summer awards; 18 Grand Opportunity matched awards; and 18 Challenge awards.

ARRA Funding: Dr. Niederhuber told members that ARRA funding for NCI's training and faculty support includes: the promotion of re-entry into biomedical and behavioral research careers ($3 M); diversity programs ($20.6 M); faculty startups ($76.2 M); and cancer research, training, career development, and education ($11.3 M). Examples of programs funded through ARRA include administrative and competitive supplements ($342 M) to support small equipment needs at individual laboratories, Phase I and II therapeutic and imaging clinical trials, Activities to Promote Research Collaborations (APRC), NCI Alliance for Nanotechnology in Cancer, and NCI Clinical Proteomic Technologies for Cancer. Examples of programs and projects funded under research and development contracts ($494 M) are: Cancer Biomedical Informatics Grid (caBIG^{TM}), expansion of The Cancer Genome Atlas (TCGA) program, Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program addressing childhood cancer, Cancer Human Biobank (CaHUB), and establishment of the Chemical Biology Consortium (CBC). The NCI funded 41 Challenge Grants ($38 M) in addition to the NIH's 18 cancer-related Challenge Grants funded, attaining an overall success rate of 20 % of grants reviewed. The NIH matched NCI's funding of 18 cancer Grand Opportunity grants ($24 M); the NCI funded an additional 33 grants ($64 M) with an overall success rate of 17 % of grants reviewed. Another mechanism supported through the ARRA is NCI's Accelerating Clinical Trials of Novel Oncologic Pathways (ACTNOW) project, through which 37 early phase clinical trials of new treatment regimens were funded. NCI obligated the majority of available NCI ARRA funds in FY09, while NIH has plans to publish several initiatives in FY10 using NIH ARRA funds.

TCGA: Dr. Niederhuber told members that initiatives increasing the base of knowledge in cancer research through the use of newer technologies include TCGA and gene sequencing. He stated that the "next generation" sequencing technology will expedite the complete sequencing of an individual's genome, thus revolutionizing medicine and effecting significant cost savings. In the pilot phase of sequencing the ovarian cancer and glioblastoma genome, three genes not previously associated with glioblastoma have been found to be directly related to the disease. TCGA is one of NIH's seven Signature Projects and involves more than 24 institutions and 100 scientists in the identification of relevant genetic alterations of cancer. ARRA funding has allowed the TCGA to study expansion of the pilot to up to 25 tumors, with the long-term goal of addressing all major cancer types and subtypes. TARGET has adopted the TCGA approach in its research on childhood cancers. These efforts are supported by the availability of high-quality tissues through the NCI's caHUB, an ongoing effort which received $60 M of ARRA funds. Dr. Niederhuber noted that TCGA has made a significant investment in obtaining and analyzing tissue from patients with cancer and mining and modeling the data for the laboratory. The new Functional Biology Consortium (FBC) will work to understand what mutations, translocations, and copy number changes mean in terms of functional biology and hence can attain translational research results more quickly. The process begins with the identification and characterization of patients through characterization centers. The information being uncovered through these technologies should be usable by administrators, physicians, patients, and scientists to help inform decision making, improve outcomes, and reduce costs.

Dr. Niederhuber informed members that Dr. Francis Collins, Director, NIH, recently identified five themes for the NIH to address, to which the NCI has long been committed. These include: 1) high-throughput technologies to understand fundamental biology and uncover causes of specific disease states; 2) translation, including the development of diagnostics, preventive strategies, and therapeutics; 3) using science to inform health care reform; 4) a greater focus on global health; and 5) reinvigoration and empowerment of the biomedical research community. Dr. Niederhuber concluded with ideas on moving the NCI forward, including an emphasis on the impact of science on patients and reducing health care costs.

In the discussion, the following points were made:

< The NCI's ability to understand disease differently and link new genetic information into clinical treatment and outcomes may help reduce health care costs.

< The NCI should develop plans to assist clinicians in interpreting genomic information for use in designing clinical treatment plans and to disseminate it to practicing oncologists.

< Members requested an update report on the trans-NIH Strategic Cancer Plan.

IV. NCI/CONGRESSIONAL RELATIONSCMS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), informed members that FY 2010 appropriations passed by the House total $31.3 B for the NIH and $5.15 B for the NCI, and the amount passed by the Senate Appropriations Committee is $30.8 B for the NIH and $5.05 B for the NCI. Recent Congressional hearings of interest to the BSA addressed breast cancer legislation and the health effects of cell phone use. Ms. Erickson also briefly reviewed legislation relevant to the NCI and CER.

V. COMPARATIVE EFFECTIVENESS RESEARCH (CER)—AHRQ AND NCI—DRS. JOHN NIEDERHUBER AND CAROLYN M. CLANCY

Dr. Carolyn M. Clancy, Director, Agency for Healthcare Research and Quality (AHRQ), provided an overview of CER as overseen by the AHRQ and NCI. Dr. Clancy observed that current challenges to the health care arena include health care spending, quality of care, large variations and inequities in clinical care, and uncertainty about best practices involving treatments and technologies, as well as translating discovery into clinical practice. Members were told that a higher cost does not necessarily result in better care. Key factors in the quality of care include focused attention to the Institute of Medicine's (IOM) quality aims: safe, timely, effective, efficient, equitable, and patient-centered care. Other factors include the public demand to know, linkage of payment to quality of care, and transparency.

Dr. Clancy said that the mission of the AHRQ is to improve the quality, safety, efficiency, and effectiveness of health care for all Americans. Members were told that AHRQ priorities include: effective health care programs, patient safety and quality, ambulatory patient safety, medical expenditure panel surveys, and other research and dissemination activities. The AHRQ is collaborating on several activities with the NCI, such as: the Prostate Cancer Intervention Versus Observation Trial (PIVOT), in which the Veterans Health Administration (VA) also is a partner; the Health Care Innovations Exchange (HCIE), which is a systematic review concerning the recruitment of underrepresented populations in cancer clinical trials; and the Consumer Assessment of Health care Providers and Systems (CAHPS) survey for cancer care.

The AHRQ Effective Health Care Program (EHCP) was created in 2005 to improve the quality, effectiveness, and efficiency of health care delivered through Medicare, Medicaid, and State Children's Health Insurance Program (SCHIP). Essential questions posed by comparative effectiveness include whether a treatment is right, and whether it is right for a particular individual. The EHCP has identified priority conditions, such as cancer, for an effective health care program, and produced technical briefs and other literature products specific to cancer, including "Particle Beam Radiation Therapies for Cancer" (September 2009) and "Comparative Effectiveness of Medications to Reduce Risk of Primary Breast Cancer in Women" (September 2009).

Dr. Clancy reminded members that the ARRA included $1.1 B for CER, of which $300 M was allocated to the AHRQ, $400 M to the NIH, and $400 M to the HHS Office of the Secretary. Examples of ARRA supported projects include: a series of coordinated clinical CER studies called the Clinical and Health Outcomes Initiative in Comparative Effectiveness (CHOICE), investment in patient registries, grants supporting dissemination and translation, and a Citizen Forum on Effective Health Care. Short-term plans include increasing public reporting, payment initiatives, common performance measures, and local collaboration. Longer range goals involve reform leading to quality improvement, rewarding and disseminating cutting edge research, better information for consumers, and effective use of health information technology (IT). Dr. Clancy said that to attain these goals it will be necessary to anticipate the longer term effects of policies, create an equal setting for all stakeholders, use research to address concerns of patients and clinicians, and address gaps in quality and issues about the most effective treatment approaches.

In the discussion, the following points were made:

< When queried about the role of the public health insurance industry in the AHRQ's support of patient-centered outcomes research, members were told that providers can use information from this research but cannot deny care based only on this research.

< Members encouraged vigilance to make certain that CER did not devolve into standardized treatments or the least expensive approach to treat patients; CER should promote, not stifle, innovation.

< Include an analysis of how treatment effectiveness varies among different racial/ethnic groups in comparative effectiveness research projects.

< The NCI's past collaborations with the AHRQ and history of supporting CER have positioned it as a leader among the NIH Institutes. Efforts to bring other ICs to an appropriate level of CER should not be allowed to impede the cancer community's progress on health care delivery.

VI. LINKING SEER AND MEDICARE CLAIMS DATABASES TO FACILITATE CER—DRS. RACHEL BALLARD-BARBASH AND NANCY L. KEATING

Drs. Rachel Ballard-Barbash, Director, Applied Research Branch (ARP), Division of Cancer Control and Population Sciences (DCCPS), and Nancy L. Keating, Associate Professor of Medicine and Health Care Policy, Harvard Medical School, described the linkage of Surveillance, Epidemiology, and End Results (SEER) data and the Medicare Claims database to facilitate CER. The SEER-Medicare data include all patients in the SEER data who are found to be Medicare eligible as well as a 5 % random sample of persons in the SEER areas who have not been diagnosed with cancer. The data include incidence, anatomic site, stage, initial treatment, demographics, cause of death, and Medicare claims for short stay hospitals, physician and laboratory services, hospital outpatient claims, and home health and hospice bills.

Members were informed that the data were first linked in 1992 for research projects on cost of care. As such, there are now over 400 publications across the cancer continuum, from screening, detection, diagnosis, and treatment through survivorship, second cancers, terminal care, and death. The SEER-Medicare data span are longitudinal from Medicare coverage until death, encompass most clinical areas, represent a diversity of geographic areas, are population-based, and include data on multiple disease conditions. Because the data are observational, however, a selection bias exists; other limitations include exclusion of non-covered services, lack of information on reasons for and the results of tests and procedures, limitation of the population to Medicare patients, and the existence of a lag time of 4 years to obtain linked data.

Dr. Keating noted that the rationale of using SEER-Medicare data for CER includes: 1) the ability to overcome the limitations of randomized controlled trials; 2) access to population-based observational data; 3) availability of longitudinal data from regions across the United States; and 4) making statistical methods available to address concerns about nonrandom assignment. Members were informed about CER studies that used the SEER-Medicare data, including investigations focused on adjuvant chemotherapy for stage III

colon cancer demonstrating a better outcome with adjuvant FU in older patients. Also, studies on 1) on minimally invasive versus open radical prostatectomy showed higher rates of incontinence and erectile dysfunction; and 2) cancer care in the VA compared to SEER-Medicare for older men noted difficulties in comparing care systems because of differences between types of both data and patients, such as high level of comorbid illness and lower socioeconomic status for veterans. Use of observational data in investigations requires approaches beyond standard regression methods.

Members were told that future plans for SEER-linked data include enhancing data resources through the addition of Part D medication data, expansion to non-SEER area registries with Medicare data, and linkage of SEER to claims data sources other than Medicare. SEER is facilitating increased use of data through additional training and technical advice, availability of SEER stat software, and the development of "SMART" software using variables from the SEER-Medicare data.

In the discussion, the following points were made:

< The NCI has instituted release criteria to ensure the SEER-Medicare data can support a proposed study. The NCI does review and provide comments on publications but cannot control the use or interpretation of data once they are released to investigators. The peer review process for publications should cover concerns about analyses and interpretation.

< Inclusion of VA data in SEER is desirable, but confidentiality concerns may make this unlikely.

< Members expressed concern about the three to four year time lag in obtaining SEER data linked to CMS. Staff noted that improving the timeframe of data acquisition is an ongoing SEER-Medicare issue.

< The NCI should consider how to prioritize SEER development to anticipate future areas of study.

< Include data on treatment toxicity in the Surveillance, Epidemiology, and End Results (SEER)-Medicare dataset. Develop a plan to improve the timeline in obtaining data. Consider a mechanism to assess the validity of SEER data and the uses to which it is put (e.g., results from studies using SEER data compared to results from similar randomized controlled trials).

VII. UPDATE: THE CANCER GENOME ATLAS—PROGRESS TO DATE -—DRS. ANNA BARKER AND MARK GUYER

Drs. Anna Barker, Deputy Director for Advanced Technology and Strategic Partnership and Mark Guyer, Director, Division of Extramural Research, National Human Genome Research Institute (NHGRI), provided an update report on TCGA. Dr. Barker informed members that the goal of TCGA is to identify changes in tumor genomes, i.e., copy number, misregulation of transcription, misregulation of translation, mutations, and epigenomic alterations, that will allow definition of cancer subtypes and subsequently stratification of patients and more effective development and targeting of therapies. TCGA initially was developed as a pilot program to evaluate and test processes needed to perform high-throughput, large-scale, disease-focused genomic characterization as well as data integration and analysis. The Program has developed strict sample collection guidelines and a set of clinical data elements for describing specimens. The first three cancer types analyzed have been glioblastoma multiforme (GBM), ovarian cancer (serous cystadenocarcinoma), and lung cancer (squamous carcinoma).

Dr. Barker provided highlights from the recent TCGA publication characterizing the tumor genomes of 206 GBM patients and identifying three genes and three core biological pathways commonly altered in these tumors. She stated that a possible mechanism by which GBM tumors become resistant to temozolomide has been identified; the mechanism involves epigenetic modifications that impact the cell's DNA repair capabilities. Initial analyses of the ovarian cancer genome have found a large number of rearrangements and amplifications, with a high frequency of *P53* mutations and *BRCA1* and *BRCA2* mutations in TCGA ovarian tumors. These data have been used to define four expression subtypes for GBM and three types of ovarian tumors that correlate with survival. This initial phase of TCGA has demonstrated the development of a

network to perform high-throughput, large-scale, comprehensive genome characterization for the discovery of new genes and to define tumor subtypes. Phase II of TCGA will involve complete characterization of 10 tumor types and lower level characterization of an additional 15 types, transition to next generation sequencing, increased tissue accrual, and the development of a quality management system for specimens.

Dr. Guyer informed members that TCGA is transitioning to next generation genomic sequencing, which allows analysis of individual DNA molecules rather than populations, and facilitates detection of rare variants, along with increasing sequencing throughput rates. TCGA has completed analysis of 144 cases of GBM, including sequencing 1,300 genes; efforts are now underway to sequence a set of 6,000 genes called the TCGA6000. Whole genome sequencing data have been generated for 12 tumor/normal pairs. For ovarian cancer, targeted sequencing has increased from an initial 2,000 genes sequenced for 26 cases of ovarian cancer to the whole exon (the entire coding capacity of the genome) being sequenced for 9 cases. Given this extraordinary level of data generation, data analysis and management present significant challenges. TCGA has developed a "card" that summarizes sequencing statistics and overall findings, such as point mutations, chromosomal rearrangements, and other relevant changes for each specimen. TCGA will continue to improve the efficiency of its data management and data analysis efforts and also plans to identify technologies that will allow sequencing of different types of specimens (e.g., paraffin-embedded); this will be necessary as TCGA starts specimen collection for some of the rarer tumor types.

In the discussion, the following points were made:

< A Roadmap project, Genotype Tissue Expression, is working in collaboration with NCI to collect tissues using rapid autopsies.

< TCGA will need to develop fair procedures to manage authorship, which is important for career advancement, particularly for younger investigators.

< Although the microenvironment is important in tumor development and treatment, TCGA currently is not structured to analyze mutations in the microenvironment.

< Better coordination of the TCGA community could involve organizing efforts around drug development, particularly biomarker discovery, and interactions with NCI Specialized Programs of Research Excellence (SPOREs) and Cancer Centers.

< TCGA should emphasize the new genes discovered versus confirming existing genes.

< Staff should 1) devise strategies to bridge the gap between TCGA data and clinicians/therapeutic delivery and to coordinate efforts and data between industry and academia; 2) include the collection of viable cells acquired after rapid autopsy (2 hours post-mortem) in TCGA; 3) share with the BSA the current list of 25 next cancers to be pursued by TCGA; and 4) provide more support to young investigators, particularly those with the mathematic and bioinformatic training that will be needed to effectively mine the data arising from large sequencing efforts such as TCGA.

VIII. BSA RFA ANNUAL CONCEPT REPORT—DR. RICHARD L. SCHILSKY

Drs. Schilsky, BSA Chair and David Maslow, Acting Executive Secretary and Associate Director, DEA, presented the annual report on RFA concepts from 1996 through June 2009. 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 %age of total NCI grants; 2) a listing of funded grants; and 3) abstracts of the funded grants in hardcopy and CD-ROM formats. The report has been generated annually since the initial BSA request in 1999 to provide background information relevant to the concept review role played by the BSA.

In the discussion, the following points were made:

< The NCI was encouraged to consider alternative ways to prepare the Board for the annual concept report review to generate a more informed discussion, such as providing a CD with the mailing or a BSA-only web site to allow review in advance of meetings.

< NCI should consider brief staff presentations that highlight concepts from the past 2 years, including funding rates and other concept data.

IX. IMAGING AND MULTI-MODALITY NAVIGATION IN INTERVENTIONAL ONCOLOGY—DR. BRAD WOOD

Dr. Brad Wood, Director, Center for Interventional Oncology (CIO), CCR, described progress made in the NCI CIO in imaging and multi-modality navigation for interventional oncology. Dr. Wood informed members that the CIO uses a multidisciplinary approach involving medical, surgical, neurologic, and other oncology fields, as well as radiation, to help define minimally invasive image-guided methods for diagnosis and treatment of locally dominant cancer. The Center also collaborates extensively with scientists around the world. In recent years, the use of improved imaging technologies and devices that ensure better tissue characterization, drug development, drug discovery, and prognosis, along with more effective therapeutic agents, has allowed a shift away from surgery to less invasive procedures as well as better targeting of chemotherapeutics to the tumor site.

Members were told that improved image-guided drug delivery techniques including radiofrequency ablation with heat-deployed nanoparticle liposomes (drug is released at 39^{o}C), radiolabeled drug-releasing beads (deposit drug over time and in specific locations), and high intensity focused ultrasound (used to augment perfusion and extravasations) will allow use of smaller doses of drugs since the dose can be more precisely targeted. These techniques also can be used to generate high regional doses of chemotherapy, avoiding systemic toxicity. Targeting ligands also can be added to drug delivery nanoparticles to improve precision.

Dr. Wood stated that imaging improvements can reduce the number of invasive procedures involved in cancer treatment. Combining magnetic resonance imaging (MRI) with ultrasound provides more accurate diagnosis and staging of prostate cancer. Better imaging techniques and devices such as a steerable bronchoscopy catheter have made it easier to learn and perform airway biopsies and tumor ablation. Integration of robotics and computed tomography (CT)-guided ablation have been used to better position needles for biopsy and laser treatment. These imaging techniques also can be used to directly visualize the effects of a drug on the tumor to determine whether the treatment is effective.

In the discussion, the following points were made:

< The CIO was encouraged to consider combination therapies, including co-loading particles with heat shock response inhibitors such as the HSP90 inhibitor.

< Beads delivering agents are considered devices by the U.S. Food and Drug Administration (FDA) and can be left in patients following the clinical intervention.

< The CIO was encouraged to explore the potential of these technologies to introduce novel drugs safely into tumors prior to their surgical removal to provide broader information about the effects of the drugs and the disease itself.

X. RFA/COOPERATIVE AGREEMENT CONCEPTSCPRESENTED BY NCI PROGRAM STAFF

Division of Cancer Treatment and Diagnosis (DCTD)
The Blood and Marrow Clinical Trials Network (RFA/Coop. Agr.)

Subcommittee Review. Dr. Curt I. Civin, Associate Dean for Research, University of Maryland School of Medicine, Director, Center for Stem Cell Biology & Regenerative Medicine, and Professor of Pediatrics, told

members that the Subcommittee supported the concept reissuance. Dr. Civin noted that the Blood and Marrow Clinical Trials Network (BMCTN) is co-supported by the NCI (30%) and National Heart, Lung and Blood Institute (NHLBI) (70%). All major transplant institutions support and vigorously participate in the network, conducting numerous trials to improve bone marrow transplants, including improving immune reconstitution and the prevention of infection, reducing regimen related toxicity, and identifying the best tissue source of stem cells. Members were told that program staff had responded satisfactorily to the Subcommittee's concerns.

The first year cost is estimated at $3.5 M for 16 U01 center awards and 1 Data and Coordinating Center (DCC), with a total cost of $18.5 M for 5 years for the NCI.

Motion. A motion to concur on the DCTD's RFP/Coop. Agr. entitled "The Blood and Marrow Clinical Trials Network" was approved unanimously.

Division of Cancer Prevention (DCP)
Community Clinical Oncology Program (RFA/Coop. Agr.)

Dr. Lori Minasian, Chief, Community Oncology and Preventive Trials Research Group, Division of Cancer Prevention, informed members that the Community Clinical Oncology Program (CCOP) network provides access to state-of-the-art cancer care by linking community hospitals and physicians to NCI-designated Cooperative Groups and Centers to help accrue patients and at-risk people to NCI-approved treatment and cancer control clinical trials. Dr. Minasian stated that in FY 2009, funded grants included 47 CCOPs, 14 minority-based CCOPs (MB-CCOPs), and 12 research bases, all of which involved nearly 3,500 physicians and 395 hospitals. Since 1983, the CCOP has been responsible for the accrual of more than 235,000 patients on NCI clinical trials; nearly 140,000 on treatment trials and 96,000 on prevention and control trials.

Members were told that an external review panel evaluated the CCOP and MB-CCOP and determined that both programs had successfully met and exceeded their major goals. The panel recommended that a strategic planning process should involve physicians, CCOP and MB-CCOP administrators, research base investigators, and external experts, and that the process should align the infrastructure and incentives with the changing nature of clinical trials. Efforts have been made to engage other Practice Based Research Networks (PBRNs), including HMO networks, as well as define eligibility criteria for MB-CCOPs. Other suggestions from the panel included expanding program goals to improve the efficiency, productivity, and collaboration in the design and conduct of clinical trials, and develop metrics beyond accrual, such as patients screened for complex studies, collection of biospecimens, and operational efficiency.

Subcommittee Review. Dr. Kathleen Mooney, Louis S. Peery, M.D., and Janet B. Peery Presidential Endowed Chair in Nursing Research Professor, University of Utah College of Nursing, informed members of the Subcommittee's unanimous support for the reissuance. Dr. Mooney noted that the program will support three new CCOPs and an additional research base; this will increase the CCOP to its traditional number of investigators and further support prevention and control trials and designs. The Subcommittee supported the evaluation panel recommendations and encourage program staff to use strategic planning to ensure its viability for the next 5 to 10 years as both science and the health care environment change.

First year cost is estimated at $3.3 M for 4 U10 awards and a total cost of $13.6 M for 3–5 years.

In the discussion, the following point was made:

< The community and NCI recognize that clinical trials will increase in complexity and additional resources will be needed. The CCOP is establishing a review panel to consider this issue, as well as examining the accrual incentives.

Motion. A motion to concur on the DCP's RFP/Coop. Agr. entitled "Community Clinical Oncology Program" was approved with 20 yeas, no nays, and 1 abstention.

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

Subcommittee Review. Dr. Victor J. Strecher, Professor and Director, Center for Health Communication Research, Department of Health Behavior and Health Education, University of Michigan School of Public Health, expressed the Subcommittee's unanimous support for the reissuance. Dr. Strecher informed members that the MB-CCOP is a targeted intervention within the overall CCOP program that focuses on enrolling minority patients on clinical trials. The eligibility criteria state that 40% of the accrual must be minorities and underserved patients. The program allows the NCI to promote health disparities research, receive recognition in particular communities and hospitals that are serving minority populations, and identify research questions that are relevant to their populations.

The first year cost is estimated at $2 M for 5 U10 awards with a total cost of $6.2 M for 3 years.

In the discussion, the following point was made:

< Future evaluation of the program's achievements will consider its impact on bringing novel therapies rapidly to minority populations.

Motion. A motion to concur on the DCP's RFP/Coop. Agr. entitled "Minority-Based Community Clinical Oncology Program" was approved with 20 yeas, no nays, and 1 abstention.

Division of Cancer Treatment and Diagnosis (DCTD)
Preclinical Pharmacokinetic and Pharmacological Studies with Anti-Tumor and Other Therapeutic Agents (RFP)

Dr. James H. Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), described an RFP to renew contracts supporting NCI's preclinical pharmacology and toxicology drug development activities. Dr. Doroshow informed members that preclinical toxicology and pharmacologic studies can help detect toxicity and optimize dosing regimens, and are required for Food and Drug Administration (FDA) Investigational New Drug Applications (INDs). The NCI has recently restructured its candidate drug development activities to make this testing more accessible. The NCI Experimental Therapeutics Development (NeXT) program incorporates existing programs such as the Rapid Access to Interventional Development (RAID) project and the Drug Development Group. The new CBC initiative and phase 0 trials will also be supported by these contracts. Program activities supported by NCI's Pharmacology and Toxicology RFP include pharmacokinetic and pharmacodynamic evaluations, formulation development, range-finding toxicology, and later stage preclinical development of monoclonal antibodies, recombinant proteins, and gene therapy agents.

During the current funding cycle, preclinical pharmacology and toxicology contracts were used to analyze 74 candidates, and INDs have been filed for 15. Generating pharmacology and toxicology data required for IND filing costs between $750,000 and $1.5 M for small molecules and more for biological agents. In September 2009, the FDA's Oncologic Drug Advisory Committee approved one candidate, depsipeptide, for treatment of cutaneous T-cell lymphoma. The contracts also have been used to analyze and develop an assay for the pharmacokinetics of a single oral dose of the Poly (ADP-ribose) polymerase (PARP) inhibitor ABT-888. Additional capacity has been projected to cover any increased work from NeXT and NIH.

Subcommittee Review. Dr. Timothy J. Kinsella, Director, Stony Brook University Cancer Center, The Joel Strum Kenny Professor of Medicine and Radiation Oncology, Stony Brook University School of Medicine, said that the Subcommittee was enthusiastic and unanimously supportive of the RFP for the pharmacology contract. Dr. Kinsella stated that all of the subcommittee questions were addressed in a distributed addendum. Even so, he noted that there was a concern regarding the out-year commitment, given the unstable economy and uncertainties about future NCI funding. Dr. Doroshow responded that the proposed budget is a ceiling and spending is dependent upon need.

The first year cost is estimated at $3.3 M for 7 N01 awards and total cost of $18.2 M for 5 years.

In the discussion, the following point was made:

< Because of restrictions stipulated by the Bayh-Dole Act, intellectual property for drug candidates remains with the investigator. The NCI cannot profit from drugs that it helps bring to market.

< Consider incorporating TCGA data into NCI drug development activities. Also pursue development of trials that simultaneously test two or more independent agents (combination therapy), particularly trials beyond Phase I toxicology testing and engagement of pharmaceutical companies in such trials.

Motion. A motion to concur on the DCTD's RFP entitled "Preclinical Pharmacokinetic and Pharmacological Studies with Anti-Tumor and Other Therapeutic Agents" was approved with 19 yeas, 2 nays, and no abstentions.

Preclinical Toxicology of Drugs Developed for Cancer and Other Diseases (RFP)

Dr. Doroshow stated that the NCI's existing toxicology contract developed an improved intermittent dosing schedule for depsipeptide, which had been dropped from further development because of severe cardiotoxicity detected in preclinical studies. The new dosing schedule was efficacious and significantly less toxic; this work convinced the FDA to allow the compound to move forward to clinical testing. The NCI toxicology contract also was used to develop a series of pharmacodynamic probes to generate data on idenoisoquinolines, which are topoisomerase I inhibitors that are less toxic than topotecan, and to select the best analogue. These contracts support an integrated program of pharmacokinetics, pharmacodynamics, efficacy, and safety studies that bridge the gap between discovery and the development of agents for human clinical trials.

Members were told that substantial increase has been requested to increase capacity to 15-20 projects per year due to the new CBC effort. The NCI will monitor the success of this project using metrics such as numbers of INDs and New Drug Applications (NDAs) filed and successful early phase studies that provide clear evidence of proof of principle.

Subcommittee Review. Dr. Kinsella said that there was enthusiasm and unanimous Subcommittee support for reissuance of the toxicology contract. Toxicology studies are an important part of drug development activities, and the reissuance is justified based on previous productivity. The Subcommittee believed that reorganization to form the NeXT program will improve utilization of both contracts.

First year cost is estimated at $9.2 M for 6 N01 awards and total cost of $52.1 M for 5 years.

In the discussion, the following points were made:

< Board members encouraged the NCI to incorporate TCGA data into its drug development activities.

< The DCTD was encouraged to develop ways to assess the efficacy of drug combinations.

Motion. A motion to concur on the DCTD's RFP entitled "Preclinical Toxicology of Drugs Developed for Cancer and Other Diseases" was approved with 19 yeas, 1 nay, and no abstentions.

XI. THE CANCER INITIATING CELL AND STEM CELL BIOLOGYCDRS. ROBERT WILTROUT, IRVING L. WEISSMAN, THEA TLSTY, KATHLEEN KELLY, JONATHAN VOGEL, AND RONALD MCKAY

Introduction

Dr. Robert Wiltrout, Director, CCR, introduced Drs. Irving L. Weissman, Director, Stanford University Comprehensive Cancer Center, Stanford University; Thea Tlsty, Professor of Pathology, University of California at San Francisco; Kathleen Kelly, Chief, CCR Cell and Cancer Biology Branch; Jonathan Vogel, Senior Investigator, CCR Dermatology Branch; and Ronald McKay, Chief, Laboratory of Neurological

Disorders and Stroke, National Institute of Neurological Disorders and Stroke (NINDS). Dr. Wiltrout informed members that the special session on cancer initiating cells and stem cell biology was designed to provide an overview of the relationship between embryonic stem (ES) cells, tissue stem cells, and cancer cells, as well as the role of cancer stem cells in disease progression and resistance to therapy.

Normal and Neoplastic Stem Cells

Dr. Weissman informed members that although cancer stem cells exist, cancer arises in progenitor cells that acquire a stem cell-like capacity to self-renew. Treatment with therapies that target the tumor mass may or may not kill stem cells, which will result in recurrence. The development of cancer stem cells can be traced in hematopoietic cells, for which the hierarchy of development from hematopoietic stem cells (HSCs) to multipotent progenitor to generation of all myeloid and lymphoid lineages is known. Leukemia arises from mutations in progenitor cells that give these cells the capacity to self-renew. Initiating mutations or translocations arise in HSCs and can lead to myeloproliferative disorders, but not necessarily leukemia. Because HSCs self-renew, these mutations become fixed in the population; additional mutations may occur in daughter cells that, together with the initiating mutation, lead to leukemia.

Analysis of myeloid leukemia cells found increased expression of CD47, which is normally expressed only on young red blood cells and allows cells to escape phagocytosis by macrophages. CD47 is expressed as HSCs mobilize and exit the sinusoidal space to allow them to evade the sinusoidal macrophages; CD47 expression is shut down once the cells have established a niche. It is expressed broadly on all AML subtypes, and high expression of CD47 in AML patients is associated with poor survival. SIRP mediates interactions between CD47 and macrophages, and blocking this interaction with anti-CD47 antibody allows phagocytosis of AML stem cells. Treatment with anti-CD47 antibody resulted in clearance of AML cells from the bone in mice; combining anti-CD47 antibody with rituximab, which blocks CD20, resulted in potent phagocytosis of NHL cells. CD47 is expressed on other cancer cells, including bladder and ovarian cancer, melanoma, and medulloblastoma, and is associated with poor survival. Experiments have shown that treating bladder and ovarian cancer stem cells with anti-CD47 antibodies facilitates phagocytosis of these cells.

In the discussion, the following points were made:

< Xenografting cancer cells often results in selection of a stem cell phenotype. This could be due to clonal competition and selection pressures conferred by the microenvironment.

< Certain subclasses of macrophages may be more efficient at killing cancer stem cells, but additional work is needed to understand the differences among subclasses.

Emergent Properties Common to Both Stem Cells and Tumor Cells

Dr. Tlsty described the distinguishing characteristics of stem cells including the ability to self renew, give rise to cells of multiple lineages, and respond to injury. As stem cells undergo lineage differentiation, they activate genes required for a specific lineage which are then locked into place and the cells become differentiated. Both stem cells and cancer cells share this epigenetic plasticity or the ability to reprogram the genome in a heritable fashion. Dr. Tlsty described her laboratory's work on a population of cells that can evade normal growth arrest signals with the silencing of *P16* and are also found in normal breast tissue. Expression profiling to compare cells with silenced *P16* to cells with active *P16* found differences in expression of more than 500 genes involved in stem-cell self-renewal, chromatin remodeling, differentiation, and response to deoxyribonucleic acid (DNA) damage. The *P16*-silenced cells also developed aneuploidy, which is observed in a number of cancers.

Repression of the *p16/pRb* pathways turns on epigenetic remodeling and targets the specific loci involved in differentiation. Silencing of *P16* resulted in upregulation of the polycomb protein EZH2, which has DNA methyltransferase activity, and subsequent hypermethylation of *HOXA9,* which controls lactational differentiation. To examine the effect of the microenvironment on methylation, *P16*-silenced cells were exposed to a wound environment to induce an epithelial-to-mesenchymal transition. Expression of e-

cadherin, which is frequently methylated in breast cancer, was decreased, cell motility was increased, and the cells exhibited a mesenchymal phenotype. Methylation of the e-cadherin promoter occurs as a *de novo* event rather than from selection of preexisting cells with methylated promoters. This work has shown that DNA methylation events can occur as a result of transcriptional repression of *P16* and are deterministic, rather than random. Cells can be programmed by their microenvironment to undergo phenotypic and gene expression changes that are associated with the targeted *de novo* epigenetic alterations important in tumor progression.
In the discussion, the following point was made:

< TCGA might provide important patient data that support the role of epigenetic changes in carcinogenesis, which may lead to therapeutic opportunities.

Modeling *PTEN* and *P53* Function in Mouse Prostate

Dr. Kelly described efforts to identify prostate cancer stem cells and analyze their roles in prostate cancer initiation and metastasis. A prostate epithelial cell mouse model was used, in which the tumor suppressors *PTEN* and *P53* were specifically deleted (*PTEN*-deleted cells), to determine the mechanistic effect of specific gene mutations on prostate progenitor populations. This model is relevant to human disease since up to 90% of metastatic tumors have these mutations. In tissue culture experiments, *PTEN*-deleted cells form protospheres that give rise to 30 % more progenitors than wild type protospheres, and demonstrate perturbations in self renewal and differentiation. The *PTEN*-deleted protospheres also expressed altered drug sensitivity to *AKT* pathway inhibitors and to androgen antagonists, unlike the wild type progenitors.

Analysis of prostate cancer metastasis in mouse models is difficult because the primary tumor tends to be lethal before metastases develop. *PTEN*-deleted progenitor cells transplanted directly into the prostate form large tumors, but no metastasis occurs. However, a clone derived from a orthotopic adenocarcinoma with an immature prostate progenitor phenotype was highly metastatic to the lymph nodes and lung. Direct injection of cells leads to adenocarcinoma, while co-injection of matrigel leads to presence of tumor cells with a basal phenotype. These cells will be used to identify mutations in signaling pathways that distinguish between metastatic and tumor-initiating phenotypes.

In the discussion, the following points were made:

< The biological events important for metastasis in prostate cancer likely differ greatly from events occurring during tumor initiation.

< The cellular subsets within prostate cancers that grow in bone could be explored in SCID/hu mice, which are immunodeficient mice with humanized bone. These mice could be used to determine the types of human prostate cancer cells that metastasize to bone and analyze how they colonize bone.

Tumor Initiating Cells in Human Cutaneous Squamous Cell Carcinoma

Dr. Vogel explained that squamous cell carcinomas (SCC) have a heterogeneous morphology with a developmental hierarchy of proliferating and differentiating cells that may be maintained by a distinct population of cancer stem cells, or tumor initiating cells (TIC), with the ability to self-renew. SCCs have cell populations that express differentiation markers within the inner layer of cells, while an outer layer of proliferating cells express Ki67 which marks dividing cells.

When cells from fresh human SCCs are grown in tissue culture, they form large spheroid colonies, in contrast to the flat monolayer formed by normal keratinocytes. The spheroid colonies can be serially passaged with no increase or decrease in colony number, suggesting that each colony has only one or two colony-forming cells. Human SCCs can be successfully xenografted onto immune-compromised mice if the stroma at the xenograft site is extensively humanized, but relatively large numbers of cells are required. A cell surface marker, CD133, was expressed on scattered cell clusters in the outer proliferating layer of the SCC tumor, which represented less than 1 % of SCC cell population. Xenografting a pure population of CD133 cells from SCC tumors resulted in tumor formation when as few as 100 cells were transplanted, representing a greater than 100-fold enrichment in tumor initiating capacity. The size of the tumor also

correlated with the number of CD133+ cells transplanted. The grafted cells could be isolated and serially implanted in a second recipient to form tumors with the original morphology, indicating that these cells have the stem cell ability of self renewal. Thus, a small sub-population of human CD133+ cells is highly enriched for TIC in human SCC. These cells may be useful for understanding how normal tissue development is altered in cancer and how the stromal environment influences TIC behavior, ultimately leading to identification of therapeutic targets.

In the discussion, the following points were made:

< Given the occurrence of aggressive SCC in renal transplant patients, the influence of the microenvironment and immune system on SCC should be examined.

< A member recommended other immunodeficient mouse models (e.g., NOD/SCID gamma) be used to explore the effects of different components of the immune system on SCC development.

Using Human Stem Cells To Understand and Treat Disease

Dr. McKay described how embryonic stem (ES) cells show promise for answering questions about development and cancer biology. Whole transcriptome characterization of undifferentiated human ES cells has shown that cells from different laboratories have slightly different expression profiles, indicating genetic diversity. Human ES cells can be prompted to differentiate, and whole transcriptome analysis of induced pluripotent stem (IPS) cells showed that the expression profiles of the induced cells closely resembled those from the related adult tissue, indicating that ES cells can be successfully reprogrammed to differentiate.

The expression patterns of several genes were analyzed to determine whether their induction in reprogrammed stem cells recapitulated normal developmental expression. *EZH2* is highly expressed in undifferentiated tissues but is switched off at the time somatic stem cells develop. This transition is recapitulated in IPS cells, and aberrations in this process may have a role in some cancers. *P53* also is regulated appropriately in IPS cells. Analysis of Glutathione S Transferase (*GST1)* expression levels across a number of ES cell lines showed that expression levels vary in ES cells derived from different sources, as is observed in the human population where 30% of the population does not express *GST1*. Expression of *MGMT*, which is controlled epigenetically by promoter methylation, is similarly variable.

The ability to accurately reprogram ES cells implies that cancer cells, which may arise as a result of disruption in the differentiation process, also could be reprogrammed to terminally differentiate. ES cells can acquire genetic changes common to precancerous conditions. Advances in stem cell biology will provide the understanding of tumor initiation required to develop new targeted therapies for cancer.

In the discussion, the following points were made:

< Although low levels of *GST1* expression appear to be linked to prostate cancer risk, this may not be a useful marker since other members of the *GST* gene family may compensate for low levels of *GST1*. A panel of *GST* markers, encompassing the entire gene family, might be more informative.

< Controlled mutagenesis could be used to identify genetic changes important for carcinogenesis. Work with ES cells also can help define differentiation transitions that may indicate potential therapeutic targets.

XII. ADJOURNMENTCDR. RICHARD L. SCHILSKY

There being no further business, the 44th regular meeting of the Board of Scientific Advisors was adjourned at 12:00 p.m. on Tuesday, 3 November 2009.

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

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