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

42nd Meeting

BOARD OF SCIENTIFIC ADVISORS

Minutes of Meeting

March 2–3, 2009
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
March 2-3, 2009

The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 42nd meeting on Monday, 2 March 2009, at 8:00 a.m. in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Robert C. Young, Chancellor, Fox Chase Cancer Center, presided as Chair. The meeting was open to the public from 8:00 a.m. until 4:50 p.m. on 2 March for the NCI Director's report; a report on NCI Congressional relations; and consideration of request for applications (RFAs) new and reissuance concepts presented by NCI Senior staff. The meeting was open to the public from 8:30 a.m. on 3 March until adjournment at 11:44 a.m. for reports from the Breast Cancer and Environment Research Centers (BCERCs), a status report on the Community Network Program (CNP), an update on the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) Program, and a scientific progress update on Transdisciplinary Research on Energetic and Cancer (TREC).

BSA Board Members Present:

Dr. Robert C. Young (Chair)
Dr. Christine Ambrosone
Dr. Andrea Califano
Dr. Michael A. Caligiuri
Dr. Curt I. Civin
Dr. Susan J. Curry
Dr. William S. Dalton
Dr. Todd R. Golub
Dr. Leland H. Hartwell
Dr. James R. Heath
Dr. Mary J. C. Hendrix
Dr. Marc A. Kastner
Dr. Timothy J. Kinsella
Dr. Kathleen H. Mooney
Dr. James L. Omel
Dr. Edith A. Perez
Dr. Richard L. Schilsky
Dr. Robert D. Schreiber
Dr. Ellen Sigal
Dr. Bruce W. Stillman
Dr. Louise C. Strong
Dr. Jane Weeks

Board Members Absent:

Dr. Paul M. Allen
Dr. Kirby I. Bland
Dr. Robert B. Diasio
Dr. Kathleen M. Foley
Dr. Sanjiv S. Gambhir
Dr. Joe W. Gray
Dr. Leroy Hood
Dr. Christopher J. Logothetis
Dr. Stuart L. Schreiber
Dr. Victor J. Strecher
Dr. Jean Y. J. Wang
Dr. Irving L. Weissman
Dr. James K. Willson

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. ROBERT C. YOUNG

Dr. Robert C. Young called to order the 42nd 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 6–7 NOVEMBER 2008 MEETING MINUTES— DR. ROBERT C. YOUNG

Motion: The minutes of the 6–7 November 2008 meeting were approved unanimously.

Motion: A motion to accept the proposed dates for future BSA meetings was seconded and approved unanimously.

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

FY 2009 Omnibus Appropriations Bill. Dr. John Niederhuber, Director, NCI, welcomed members. Dr. Niederhuber announced that the NCI has been directed by the House Appropriations Committee to name a Fellowship in Surgical Pathology the "Alan S. Rabson Award." Members were reminded that the NCI continues to operate under a Continuing Resolution (CR). The FY 2009 Omnibus Appropriations Bill, which has been passed by the House and is under consideration by the Senate, includes $30.3 B for the NIH and $4.97 B for the NCI. The bill reflects increases of 3.1 and 2.9 percent over FY 2008 levels for the NIH and NCI, respectively.

The American Recovery and Reinvestment Act (ARRA) of 2009. Dr. Niederhuber said that the ARRA allocates $10.4 B to the NIH. It recognizes the economic and health impact of investing in biomedical and behavioral research, aims to spur advances in science and health, and will impact more than 3,000 institutions in 50 states. Dr. Niederhuber recognized Senator Arlen Specter's (R-PA) role in ensuring inclusion in the Act of $8.2 B to the NIH for research, of which $7.4 B will be transferred to the NIH Institutes and Centers (ICs) and the NIH Common Fund, including an estimated $1.26 B to the NCI. Members were told that an additional $500 M is expected to be distributed for facility construction and renovation on the NIH campus; $1 B for extramural construction; $300 M for large shared instrumentation; and $400 M for comparative effectiveness research. The funding will support various grant mechanisms, such as new and competing individual investigator grants (R01s) and innovative activities through the NIH Challenge Grant Program. Dr. Niederhuber expressed the NCI's commitment to ensure that its applications, awards, and success rates of competing research project grants (RPGs) remains balanced.

Other funds pertinent to cancer research include: $2 B to the U.S. Department of Health and Human Services' (HHS) Office of National Coordinator for Health Information Technology; and $1 B for HHS' Prevention and Wellness Fund, of which $650 M is intended to carry out evidence-based clinical and community-based prevention and wellness strategies. The current plan to allocate stimulus funds aims to support the best scientific opportunities and projects with the broadest impact, as well as work that can be accomplished in 2

years. Accountability and transparency regarding these funds is paramount, with an unprecedented level of required reporting; details about the money spent will be available at www.recovery.gov.

Priorities of the New Administration. Dr. Niederhuber said that the Administration's emphasis on science, which is welcomed by the science research community, is illustrated through the appointment of Dr. Steven Chu as Energy Secretary and Dr. John Holdren as Science Advisor to the President. Other notable appointments include Drs. Eric Lander and Harold Varmus as Co-Chairs of the President's Council of Advisors on Science and Technology. The Administration's priorities encompass health care coverage and affordability, access and quality of care, innovation through science, and recruitment and training of the next generation. The NCI is addressing these priorities through its networks of cancer centers, the NCI Community Cancers Center Program (NCCCP), and Cancer Biomedical Informatics Grid (caBIG™) and BIG Health™ Consortium, as well as its biology-to-translation infrastructure, and clinical applications based on evidence.

Dr. Niederhuber referred members to the NCI's annual Bypass Budget report that articulates to Congressional leadership and the public about the need to build and maintain resources and capacity in the battle against cancer. He provided an update on the September 2008 Brookings Institution Conference on Clinical Cancer Research and the follow up meeting between NCI leadership and Dr. Mark McClellan at Brookings Institution. The discussion focused on cancer as the arena for the investigation of molecular medicine, the need to build partnerships to develop knowledge in real-time situations, continue discussions with the Centers for Medicare and Medicaid Services (CMS) regarding covering expenses of diagnostic tests, and explore opportunities to co-develop diagnostic and preventive interventions.

Executive Committee (EC) Scientific Retreat. Dr. Niederhuber informed members that an EC Scientific Retreat was held in late January to discuss the current direction and future investment in cancer research. Discussions during the retreat focused on the need to: 1) conduct real-time assays of the stressors and responses that initiate and sustain cancer; 2) model the evolution of cancer with a focus on alterations in the microenvironment; and 3) understand the epigenetic changes that control the type and number of cancer cells. The NCI faces a number of challenges, including knowing where science and technology is leading cancer research, improving its research portfolio, and conducting science at the intersection of disciplines. Members were told that the NCI will continue to work across divisions, use resources effectively, and ultimately translate findings to the patient.

In the discussion, the following points were made:

- Details about contractual requirements mandated by the ARRA, including those governing construction or renovation proposals, are unknown and will be shared as they become available.
- Further communication will be provided regarding ARRA cancer related comparative effectiveness grants and oversight governance by the AHRQ and HHS, in addition to the NIH, when more information is available.
- Funds provided through the ARRA must be used for new science and hiring new staff and cannot offset budget reductions of ongoing research grants.
- The first deadline for the submission of Challenge Grants applications under the ARRA will be in April 2009 to ensure that funding occurs by the end of FY 2009.
- Members expressed concern about the sustainability of projects that initially are funded under the ARRA and the requirement to spend the funds within a short time period. Members were told that the NCI leadership recognizes the complexities involved and has developed models to help guide funding decisions and risks.
- Administrative supplements will address scientific themes, and the review and approval of these themes by appropriate experts and staff will be carefully documented.

IV. NCI/CONGRESSIONAL RELATIONS—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OCGR), informed members that the Omnibus Appropriations for FY 2009 which was passed by the House on 25 February is scheduled for Senate consideration. Legislation introduced in the 111th Congress includes the Children's Health Insurance Program Reauthorization Act, which was signed into law on 4 February, and several health information technology (IT) bills. Four bills have been reintroduced from the 110th Congress, including legislation on childhood brain tumor prevention, access to cancer clinical trials, pancreatic cancer, and pain care. Ms. Erickson concluded by noting that implementation is underway regarding bills passed during the 110th Congress, particularly the Breast Cancer and Environment Act and the Conquer Childhood Cancer Act.

V. RFA/COOPERATIVE AGREEMENT NEW CONCEPTS—PRESENTED BY NCI STAFF

Office of the Director
Phase I: Strengthening Capacity for Research for HIV-Associated Malignancies in Africa (RFA)

Dr. Robert Yarchoan, Director, Office of HIV and AIDS Malignancy (OHAM), informed members that the RFA is intended to enhance the research capacity in Africa to allow U.S. investigators to develop and manage sustainable collaborations in Africa. Kaposi sarcoma (KS) associated herpes virus (KSHV/HHV-8) is endemic in Africa fueling a KS epidemic, and a number of other major cancers common in sub-Saharan Africa are associated with HIV infection. Dr. Yarchoan informed members that a key barrier towards developing sustainable collaborations is the lack of trained partners in Africa. Over the past three years, the NCI has partnered with other NIH institutes and Centers (ICs) to develop an international HIV/AIDS-related malignancy portfolio that includes supplemental funding to the Centers for AIDS Research (CFAR) and AIDS International Training and Research Program (AITRP).

The NCI and the Fogarty International Center (FIC) have partnered in the development of this Phase I RFA with the goal of training African investigators and building multidisciplinary research teams. Each application must include a U.S. principal investigator (PI) and an African co-PI. Options for training include short-term training in the United States for individuals with professional degrees, long-term training in the United States that include postdoctoral and degree training, and in-country training in Africa. Grantees must provide documentation of the impact of the training program, as well as tables with specific documentation. The NIH Office of AIDS Research (OAR) has endorsed this project as high-priority AIDS research. Phases I and II will help African institutes to emerge as independent partners for further studies with U.S. investigators.

Subcommittee Review. Dr. Curt Civin, Associate Dean for Research, University of Maryland School of Medicine, expressed the Subcommittee's support for the RFA concept. Dr. Civin stated that the full RFA should include a more in-depth discussion of how research in Africa will help address HIV and other virally related malignancies in the United States. Members were informed that the National Institute of Allergy and Infectious Diseases (NIAID) is leading efforts on the reduction of HIV itself with the NCI program addressing HIV malignancies. The AITRP has demonstrated that an applicant pool exists and that African PIs can develop successful research programs. This concept differs from the AITRP in that it emphasizes a project-based research team.

The first year cost is estimated at $4 M for 6–7 D43 awards and a total cost of $12 million for 3 years.

In the discussion, the following point was made:

- The NIAID and NCI collaborate on multiple AIDS research programs, including the CFARs, which the NIAID oversees and to which the NCI provides supplements for AIDs related malignancies.

Motion. A motion to concur with the Office of the Director's (OD) Request for Application (RFA) concept entitled "Phase I: Strengthening Capacity for Research for HIV-Associated Malignancies in Africa" was approved unanimously.

Division of Cancer Biology and Division of Cancer Prevention
Fundamental Understanding of the Biology of Estrogen Receptor Negative Breast Cancer Among Various Racial and Ethnic Groups (RFA/Coop. Agr.)

Dr. L. Michelle Bennett, Center for Cancer Research (CCR), informed members that estrogen receptor-negative (ER-) breast cancer tends to be more aggressive than ER+ breast cancer with an earlier age of onset, a higher incidence in minorities, poorly differentiated tumor types, high incidence of metastasis, and an inferior clinical outcome. Recommendations from the Health Disparities in Estrogen Receptor Negative Breast Cancer Think Tank include the systematic study of the biology of ER- breast cancer and identification of tumor- and stroma-specific biologic differences among racial groups. The initiative will leverage existing resources including clinically annotated breast cancer samples from cohort studies, animal models, cell lines, heterotypic three-dimensional cultures, and new imaging and molecular profiling technologies. This research will identify molecular characteristics, key genes, and signaling pathways that distinguish ER+ and ER- tumors and will help develop improved detection strategies and targeted therapies as well as improve understanding of the molecular basis for racial/ethnic disparities in ER- breast cancer incidence.

Dr. Bennett noted that the funding for this initiative would be from the Breast Cancer Stamp Act Fund. This structure will facilitate multidisciplinary collaboration and allow NCI programmatic involvement beyond normal stewardship of grants.

Subcommittee Review. Dr. Edith A. Perez, Professor of Medicine, Division of Hematology and Oncology, Mayo Medical School, and Director, Breast Cancer Program, Mayo Clinic, voiced the Subcommittee's enthusiastic support for the concept. Dr. Perez noted the need to focus on ER- breast cancer and suggested that descriptions of the breast cancer subtypes be clarified in the RFA. Questions were raised about whether each grant application must address the racial disparities in ER- breast cancer along with basic biology. In addition, the set aside may be inadequate for the type of interdisciplinary research projects being solicited.

The first year cost is estimated at $1.2 M for 3–4 U01 awards with a total cost of $6 M for 5 years.

In the discussion, the following points were made:

- The NCI will hold a pre-application conference, in which formation of multidisciplinary teams by potential applicants will be encouraged.
- Merging basic biology and epidemiologic research into a single project may be difficult given the size of the awards. However, NCI should consider allowing some studies to focus on basic biology of ER- breast cancer and others on racial/ethnic disparities.
- The NCI should consider a two step process where a group with appropriate patient population and biospecimen collections would be identified and the RFA would encourage researchers to collaborate with these groups.
- The NCI should encourage the use of modeling of signaling pathways and other analytic techniques to integrate the molecular data that these proposals will generate.

Motion. A motion to concur with the Division of Cancer Biology's (DCB) and Division of Cancer Prevention's (DCP) RFA/Cooperative Agreement (Coop. Agr.) concept entitled "Fundamental Understanding of the Biology of Estrogen Receptor Negative Breast Cancer Among Various Racial and Ethnic Groups" was approved unanimously.

Division of Cancer Treatment and Diagnosis
Cancer Immunotherapy Trials Network (CITN) (RFA/Coop. Agr.)

Dr. James H. Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), said that there is growing interest in cancer immunotherapy in both the NCI intramural and extramural research communities.

Dr. Doroshow told members that the NCI had sponsored an Immunotherapy Agent Workshop in July 2007, during which 20 of 124 agents with high potential for use in cancer therapy were ranked, based on their potential for use in multiple clinical settings, lack of availability, and potential for approval for commercial use. Translation of biologic agents to the clinic is challenging, particularly use of agents in combination. Specific challenges include biomarker use to identify appropriate patient populations, prioritization of potential agent combinations, lack of direct correlation between mouse models and human subjects, availability of agents for human trials, and the need for both investigative new drugs (INDs) and multi-institution approaches for Phase II trials.

The RFA creates a network of leading investigators in cancer immunotherapy to facilitate design and implementation of Phase I and II trials on novel agents and modalities, particularly in combination studies. It incorporates high-quality, centralized immune-monitoring services for trials, in addition to biomarker assessment and correlative studies. This single multi-PI cooperative agreement involves clinical sites, tumor immunology laboratories, and NCI intramural sites. The Cancer Immunotherapy Trials Network (CITN) will use the existing Cancer Trials Support Unit (CTSU) to serve as a central coordinator to provide flexibility, such as including ancillary sites for per patient reimbursement.

Subcommittee Review. Dr. Robert D. Schreiber, Alumni Endowed Professor of Pathology and Immunology, Washington University School of Medicine, informed members that the Subcommittee supported the concept and found the idea of centralizing cancer immunotherapy clinical trials was timely. Challenges in partnering with industry were noted, and NCI was encouraged to partner with the Cancer Vaccine Collaborative for peptide vaccines. Dr. Schreiber also noted that the criteria for success of an immunotherapy program as well as the Phase II design of immunotherapy trials may need to be redefined. Finally, the network structure should be developed so as to attract industry involvement, and a sufficient number of biologic agents should be available to study.

The first year cost is estimated at $1.6 M for 6-8 U01 clinical sites and Tumor Immunology Laboratories with a total cost of $14 M for 5 years.

In the discussion, the following points were made:

- The NCI has extensive experience in bringing together pharmaceutical and biotechnology stakeholders to address IP issues related to immunotherapy and combination studies.

- The NCI should consider a Small Business Innovation Research (SBIR) RFA to expedite the production and availability of agents, as well as promote combination clinical trials using the network.

Motion. A motion to concur with the Division of Cancer Treatment and Diagnosis (DCTD) RFA/Coop. Agr. concept entitled "Cancer Immunotherapy Trials Network (CITN)" was approved unanimously.

Division of Cancer Biology American Recovery and Reinvestment Act Initiatives

Dr. Dinah Singer, Director, DCB, informed members about two initiatives that will be supported under the ARRA: NCI Activities to Promote Research Collaboration (APRC) (Announcement) and AIDS Vaccine Program (RFA concept).

NCI Activities to Promote Research Collaboration (APRC) (Announcement)

Dr. Singer stated that this initiative expands an existing support mechanism that has been overseen by the DCB for many years. The APRC objective is to stimulate new, multidisciplinary research collaborations across the cancer research continuum. The proposed project must be novel and involve new collaborations (no collaborations in the past five years), and all principal investigators must be currently funded NCI investigators. Specifically, the APRC will provide administrative supplements to NCI grants that are funded through the following mechanisms: P01, P20, P25, R01, R33, R37, U01, U10, U19, or U54/56.

First year costs are estimated at $7.5 M for 12–15 supplements for a total cost of $15 M for 2 years, with each collaboration eligible for $100,000 direct costs with a maximum of $300,000 per consortium.

In the discussion, the following points were made:

- Although P30 and P50 mechanisms are not included, there is another competitive supplemental mechanism that might better support their studies.

- The NCI is encouraged to consider allocating additional funds to the APRC administrative supplements.

AIDS Vaccine Program (RFA)

Dr. Singer informed members that the AIDS Vaccine Program RFA concept, sponsored by DCB and OHAM, proposes to fund research on exploratory strategies for the development of either preventive or therapeutic vaccines against HIV and HIV-associated viral malignancies. Malignancies associated with KS-associated herpes virus, Epstein-Barr virus, hepatitis C virus, and certain human papilloma virus (HPV) types are found more often in people with HIV. Currently, the NCI has no initiative to promote vaccine research for HIV or HIV-associated malignancies and the AIDS Malignancy Working Group has recommended this research as a high priority area for the NCI.

First year costs are estimated at $10 M for 20-30 U01 applications for a total cost of $20 M for two years.

In the discussion, the following points were made:

- Clarification concerning the type of research solicited by this initiative is needed, including whether the development of immunogenic antigens for future vaccine development is appropriate.

Division of Cancer Control and Population Sciences and Division of Cancer Biology Stress Regulation and Tumor Biology (RFA)

Dr. Robert Croyle, Director, DCCPS, introduced the Stress Regulation and Tumor Biology RFA to fund research to identify biological mechanisms underlying the relationship between human stress physiology and cancer. A number of clinical studies suggest an association between psychosocial stress and cancer outcomes, but there is little basic science supporting these associations. Dr. Croyle responded to previous concerns regarding a lack of clinical studies and translational relevancy that were raised at the concept's original presentation to the Board in November 2008 and presented several new clinical studies. A recent meta-analysis of 330 studies found that stress-related psychosocial factors were associated with poorer survival for a number of cancers. There is a great deal of public interest in a possible relationship between stress and cancer outcome, and research sponsored by this initiative should help to identify the underlying biological mechanisms and determine whether the relationship is causal or not.

Subcommittee Review. Dr. Mary J.C. Hendrix, President and Scientific Director, Children's Memorial Research Center, and Professor, Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, expressed the Subcommittee's interest in the data but indicated mixed support for the concept. Concerns were raised about whether the clinical and animal data proved a causal association, and the ability to measure stress in a reliable and reproducible manner as well as the potentially erroneous narrow focus on stress as a mediator of cancer outcome. The concept should be clarified regarding its solicitation of basic versus clinical research.

The first year cost is estimated at $4.5 M for 10 awards with a total cost of $14.6 M for 2 years (R21) and 4 years (R01).

In the discussion, the following points were made:

- Some members felt it would be more appropriate to perform more clinical studies to determine if the relationship between stress and cancer could be explained by other factors or if the clinical efficacy evidence of stress interventions was strong enough to warrant intensive basic research.

- The existing evidence justifies further research, but the size of the community involved in current studies may be insufficient to develop the infrastructure suitable for the RFA mechanism.

- Members supported solicitation of both clinical and basic studies with funding going to the strongest research proposals. However, the clinical aspect in the RFA needs further development.

Motion. A motion to concur with the Division of Cancer Control and Population Sciences (DCCPS) and DCB's RFA concept entitled "Stress and Tumor Biology" was disapproved with 7 yeas, 12 nays, and 1 abstention.

Division of Cancer Control and Population Sciences
State and Community Tobacco Control Policy and Media Research (RFA)

Dr. Croyle informed members that the RFA concept addresses high-priority research gaps on the impact of secondhand smoke policies, the effect of tobacco excise taxes and pricing policies on various populations, and the development of mass media interventions to counter the tobacco industry's promotional practices. He noted that there are 45 million adult smokers (21% of adults) and 3 million youth smokers (20% of youth) in the United States, and disparities remain among racial/ethnic, income, educational, and occupational groups. The concept provides an opportunity to determine optimal population-level interventions to reduce tobacco use, devise effective strategies to better reach underserved populations, and obtain insight into how to counter continually evolving tobacco industry practices. National tobacco control partners include the American Cancer Society (ACS), American Legacy Foundation, Centers for Disease Control and Prevention (CDC), National Institute on Drug Abuse (NIDA), and Robert Wood Johnson Foundation (RWJF). The need for more policy and media research, particularly focusing on specific populations with states and communities being ideal research settings, was identified at a number of meetings, including an NIH State of the Science on Tobacco conference and the President's Cancer Panel: Promoting Healthy Lifestyles. This RFA supports 3-4 grants in each of three focus areas: secondhand smoke, tax and pricing policies, and mass media interventions.

Subcommittee Review. Dr. Susan J. Curry, Distinguished Professor and Dean, College of Public Health, University of Iowa, expressed the Subcommittee's enthusiastic support for this RFA, which articulates the importance of continued high-quality science to bridge research gaps in effective community tobacco control policies and media interventions. The evaluation criteria will translate into improvements of public health quickly. The concept could serve as a model for behavioral research, taking a population approach to behavior change. It forges a new way for research in that it helps stay abreast of current and evolving media advertising practices and targets resistant groups, such as addicted youth.

The first year cost is estimated at $12 M for 10–12 R01 awards for a total cost of $60 M for 5 years.

In the discussion, the following points were made:

- The NCI should consider using the U01 mechanism, rather than R01s, since coordination with other partners and the Cancer Intervention and Surveillance Modeling Network (CISNET) program may be needed.

- Members requested updates on changes in the FDA regulatory activities concerning tobacco and how NCI data and activities are used to inform regulatory decisions.

Motion. A motion to concur with the DCCPS' RFA entitled "State and Community Tobacco Control Policy

and Media Research" was approved unanimously. [Note: NCI staff concurred with the recommendation to use the cooperative agreement mechanism.]

Division of Cancer Prevention
Common Pathogenetic Mechanisms of Lung Cancer and COPD (RFA)

Dr. Peter Greenwald, Director, Division of Cancer Prevention (DCP), stated that lung cancer and Chronic Obstructive Pulmonary Disease (COPD) are leading causes of mortality, with lung cancer responsible for approximately 159,000 deaths and COPD 127,000 deaths in 2005. Smoking is hypothesized to create inflammation in the lung, contributing to the development of both conditions, although via different molecular mediators. This RFA is aimed at the population of smokers that develops both diseases.

The concept's objectives are to identify fundamental pathogenic characteristics shared by lung cancer and COPD and genotypic and phenotypic characteristics indicative of individual susceptibility. Possible applications include: 1) clarifying the co-epidemiology of lung cancer and COPD through defining clinical characteristics and molecular phenotypes and identifying shared genetic and epigenetic risk factors; 2) investigating common and disparate mechanisms involved in the pathogenesis of COPD and lung cancer, including the roles of innate and adaptive immunity, injury repair, microenvironment, and stem cells; and 3) identifying and validating biomarkers and molecular signatures to develop measures of risk, presence, severity, and progression of COPD and lung cancer as well as response to therapy. The National Heart, Lung and Blood Institute (NHLBI) currently supports a COPD Genome-Wide Association Study (GWAS) featuring a well-characterized, 10,500 person COPD cohort that might be leveraged with this initiative. The RFA is co-sponsored by the NCI and NHLBI and is designed to bring together the historically separate cancer and pulmonary research communities by strongly encouraging multiple PIs from both communities.

Subcommittee Review. Dr. Timothy Kinsella, Director, Stony Brook University Cancer Center, The Joel Strum Kenny Professor of Medicine and Radiation Oncology, Stony Brook University School of Medicine, said the Subcommittee supported the RFA concept. Dr. Kinsella stated that there may, however, be challenges in fostering effective collaboration between the NCI and NHLBI research communities. He also noted that another concern was the exclusion of animal studies, given the existence of lung cancer mouse models and smoking models.

The first year cost is estimated at $3 M for 6–9 R01 awards with a total cost of $12 M for 4 years.

In the discussion, the following points were made:

- The COPD GWAS could be used to find protective genes, given that significant numbers of people who smoke do not develop lung cancer.

- The RFA should encourage integration of data generated by the lung cancer and pulmonary research communities and the development of models, including synthesis of existing data.

Motion. A motion to concur with the DCP's RFA entitled "Common Pathogenetic Mechanisms of Lung Cancer and COPD" was approved unanimously.

Division of Cancer Treatment and Diagnosis
Support for Human Specimen Banking in NCI-Supported Cancer Clinical Trials (Cooperative Group Banks) (RFA/Coop. Agr. Reissuance)

Dr. Doroshow informed members that this limited competition reissuance request for the Cooperative Group Banks (CGB) will continue the CGB's work in collecting and distributing specimens from patients enrolled in Clinical Cooperative Oncology Group (CCOG) trials. Accomplishments include an extensive effort to harmonize standard operating procedures and prepare a central manual of operations, as well as develop a central biospecimen query system in collaboration with caBIG® for the identification and sharing of tissues.

Additional work has involved completing a common informed consent form, patient brochures, and institutional review board (IRB) information sheets, as well as efforts in access and marketing. Nearly 300 external investigators have accessed the solid tumor banks, which include more than 800,000 tumor specimens and close to 150,000 serum specimens. Research using these specimens has led to 1,350 publications and 36 patents by CGB users. An external evaluation of CGB documented the positive effect of the publications and encouraged a more rapid harmonization of procedures, increased collection of frozen specimens to meet emerging technology needs, and fair and open access to specimens.

Subcommittee Review. Dr. Todd R. Golub, Director, Cancer Program, Broad Institute of Massachusetts Institute of Technology and Harvard University, informed members that the Subcommittee supported the reissuance as a way to make clinically annotated biospecimens available for correlative analyses in the context of clinical trials. Dr. Golub stated that the effort has been successful to date, with samples collected as proposed and significant discoveries made that have influenced clinical practice. The Subcommittee supported a critical review of individual biobanking centers, and noted that the availability of clinical data in aggregate form, because of privacy issues, presents a challenge in linking such data with specific molecular data generated by the studies.

The first year cost is estimated at $8.75 M for 9 U01 awards for a total cost of $43.75 M for 5 years.

In the discussion, the following point was made:

- The Breast Cancer Intergroup has developed a model system for reviewing and approving proposals for specimen access. Other steering committees are adopting this model.

Motion. A motion was made to concur with the DCTD's RFA/Coop. Agr. reissuance entitled "Support for Human Specimen Banking in NCI-Supported Cancer Clinical Trials (Cooperative Group Banks)." The motion was approved with 20 yeas, no nays, and 1 abstention.

Division of Cancer Control and Population Sciences
Cancer Intervention and Surveillance Modeling Network (CISNET)
(RFA/Coop. Agr. Reissuance)

Dr. Croyle informed members that CISNET is a modeling consortium that develops and uses sophisticated evidence-based decision tools to understand the impact of cancer control interventions at the national population level. Members were referred to the CISNET progress report for descriptions of its systematic comparative modeling through a mathematical approach. He noted that the reissuance will:1) expand CISNET to encompass cervical, ovarian, and esophageal cancers; 2) use "upstream" modeling to understand social and economic determinants of usage, screening, treatment, and risk behavior; and 3) develop multi-scale cancer models to include molecular and cellular determinants of tumor behavior; and incorporate genomic and family history risk profiles in intervention modeling efforts. Other areas include collaborations with Early Detection Research Network (EDRN) investigators for optimizing biomarker development strategies, and an international component focused on translating trial results into clinical guidelines and public health policy. Modeling also will assist with comparative effectiveness research efforts, particularly with CISNET and cancer research serving as models for surveillance, modeling, and large clinical trials networks.

CISNET accomplishments include 18 models (5 lung, 7 breast, 3 colorectal, and 3 prostate) and 90 publications. Budget increase provides collaborative study funds and an increase to six cancer sites. External reviewers recommendations are being implemented, including pilot studies in new areas, genomic and family history risk profiles, and health disparities, along with the use of modeling to evaluate diagnostic tests.

Subcommittee Review. Dr. Curry informed members that the Subcommittee expressed unanimous support for the reissuance. CISNET is a valuable component of the NCI's portfolio and has great translational potential and nice synergy with other initiatives. The reissuance's expansion of the number of cancers and mixture of collaborating disciplines also was viewed favorably.

The first year cost is estimated at $5.4 M for up to 6 U01 awards for a total cost of $29.4 M for 5 years.

In the discussion, the following points were made:

- Concern was expressed about how modeling results might be interpreted and used by policymakers who struggle with how or if to use evidence in their decisions. Staff noted that the NCI and NIH attempt to synthesize the information and communicate it effectively, along with relevant caveats.

- CISNET could advance comparative effectiveness research by modeling the value of information obtained from several prospective clinical studies to inform the design of a randomized trial.

Motion. A motion to concur with the DCCPS' RFA/Coop. Agr. Reissuance concept entitled "Cancer Intervention and Surveillance Modeling Network (CISNET)" was approved unanimously.

Division of Cancer Prevention
Early Detection Research Network (RFA/Coop. Agr. Reissuance)

Dr. Greenwald presented the reissuance RFA concept for the EDRN whose mission is to support systematic evidence-based discovery, development, and validation of biomarkers for cancer detection, diagnosis, and prognosis. The Network is composed of biomarker development laboratories, biomarker research laboratories, clinical and epidemiological validation centers, and a data management and coordination center. He noted that it has been favorably reviewed by two external review committees, including the BSA EDRN Working Group. NCI plans to implement their recommendations on chairmanship terms and empowering the Steering Committee as a governance body. Work supported by the EDRN has led to more than 27 patents and 17 licenses, with 127 biomarkers in Phase 1 and 2 development and five biomarkers in Phase 3 studies. Separate RFAs will be used for each component with the goal of maintaining and building on the existing EDRN infrastructure and its strong collaborative network of investigators.

Subcommittee. Dr. James Heath, Elizabeth W. Gilloon Professor and Professor of Chemistry, Division of Chemistry and Chemical Engineering, California Institute of Technology, expressed the Subcommittee's support for the reissuance. Dr. Heath stated that its core strength is to take biomarker discoveries through the clinical validation process, not the biomarker discovery process. It was suggested that EDRN consider soliciting applications from the cancer community as a whole for biomarkers that should be stringently analyzed, rather than support the discovery of biomarkers within EDRN. Other members acknowledged that EDRN needs to maintain a discovery component to attract talented investigators to the program, but suggested that the validation aspect of the EDRN be emphasized. The Subcommittee commended the EDRN on the infrastructure it has developed, particularly the validation laboratories. The use of core funding to develop a biomarkers database also was commended.

The first year cost is estimated at $32 M for U01s up to 25 Biomarker Development Laboratories, 8 Clinical and Epidemiology Validation Centers, 4 Biomarker Laboratories, and 2 Data Management and Coordinating Centers for a total cost of $160 M for 5 years.

In the discussion, the following points were made:

- The EDRN should collaborate with DCB and DCP on the ER- breast cancer RFA to assist in discovery and validation of biomarkers specific for this cancer.

- The EDRN should be aware of possible conflicts of interest when validating biomarkers discovered by in-house investigators.

- The EDRN should be prepared to validate a host of different types of biomarkers submitted from the community. These biomarkers also should be validated in populations distinct from those used to

initially discover and develop the biomarkers.

Motion. A motion made to concur with the DCP's RFA/Coop. Agr. reissuance entitled "Early Detection Research Network (EDRN)" was amended with the caveat that the RFA/Coop. Agr. emphasizes validation. The amended motion was approved with 16 yeas, 2 nays, and 3 abstentions.

Office of the Director (Information Only)
SBIR Phase II Bridge Awards to Accelerate the Development of New Cancer Therapies, Medical Devices, and Diagnostics Toward Commercialization (RFA Reissuance)

Dr. Richard L. Schilsky, Professor of Medicine, Section of Hematology and Oncology, Biological Sciences Division, University of Chicago Pritzker School of Medicine, reported on the Subcommittee's review of the SBIR Phase II Bridge Award program (Phase IIB) which provides continued funding for SBIR projects addressing cancer treatment, diagnosis, or detection as companies prepare products for entry into the clinic. Dr. Schilsky informed members that the program was released in May 2008, and applications were received in September 2008 and February 2009 but no awards have been made. Thus, the Subcommittee indicated that they had insufficient information to fully evaluate the program, however, based on the apparent need for this program, it was recommended that it continue for another year. The Subcommittee requested that progress reports be given to the BSA on the SBIR Program's Phase I and II portfolios, and its Phase II Bridge activities, outcomes, and integration with other translational research mechanisms.

Dr. Niederhuber said that the SBIR program operates differently than other NCI and NIH programs, and that the notable success by the National Aeronautics and Space Administration (NASA) and National Science Foundation (NSF) in using a unique SBIR model inspired some of the changes during the past year to NCI's approach. The Phase IIB program requires that applicants raise matching dollars to the NCI's award of up to $3 M for 2–3 years of funding. The rigorous due diligence performed by venture capitalists or other strategic partners reassures the likely success of NCI's investment.

In the discussion, the following point was made:

- Legislation requires that all projects initially receive SBIR Phase I and II funding prior to applying for the Phase IIB program. Joint Phase I and II applications can be submitted to expedite the process.

VI. BREAST CANCER AND THE ENVIRONMENT RESEARCH CENTERS –DRS. DEBORAH WINN, GWEN COLLMAN, LINDA BIRNBAU, FRANK BIRO, SANDRA HASLAM, AND MS. JANICE BARLOW

Introductions—Dr. Deborah Winn

Dr. Deborah Winn, Deputy Director, DCCPS, introduced the speakers who provided a progress report on the Breast Cancer and Environment Research Centers (BCERCs): Drs. Gwen Collman, Interim Director, Division of Extramural Research and Training, National Institute of Environmental Health Sciences (NIEHS); Linda Birnbaum, Director, NIEHS; Frank Biro, Professor of Clinical Pediatrics, University of Cincinnati; Sandra Haslam, Professor of Physiology, Michigan State University; and Ms. Janice Barlow, Zero Breast Cancer.

Genesis of the Breast Cancer and the Environment Research Centers—Dr. Gwen Collman

Dr. Collman introduced the BCERCs which is an NCI and NIEHS initiative begun in 2003 on breast cancer and the environment to: 1) provide new scientific data about the effects of selected environmental stressors on the architect of the mammary gland; 2) examine the effects of exposure during life—including *in utero*, childhood, and puberty—and explore their mechanism of action; and 3) study the genetic and environmental determinates related to the timing of pubertal changes as they may make a breast more susceptible for cancer

later in life. Each center has a biology project, an epidemiology project, and a community outreach and education core, and the involvement of scientists and advocates in all parts of the project, research governance, and outreach ensures successful communication and collaboration. The four BCERCs (Bay Area, University of Cincinnati, Fox Chase Cancer Center, and Michigan State University) include scientific communities and collaborative community partners.

Perspectives from the National Institute for Environmental Health Sciences (NIEHS)—Dr. Linda Birnbaum

Dr. Birnbaum informed members about the NIEHS $171 M current investment in cancer research. The intramural program includes: a Laboratory of Molecular Carcinogenesis with over 70 scientists; epidemiological research, such as the Sister Study, a longitudinal perspective study recruiting 50,000 women with breast cancer who have a sister who does not have breast cancer; and the Genetic Alterations in Cancer database. The NIEHS leads the National Toxicology Program, a multi-agency effort involving the NCI, National Institute for Occupational Safety and Health (NIOSH), and FDA. The program conducts bioassays, prepares a biennial report on carcinogens and technical reports, and supports extramural research efforts on carcinogens. Extramural research on the environment and cancer covers environmental carcinogenesis, susceptibility, epigenetics, and epidemiology.

Epidemiology Project—Dr. Frank Biro

Dr. Biro described a BCERC epidemiologic study on the link between factors associated with the onset of puberty and later risk for breast cancer. The aim of the epidemiology project is to examine the determinants of puberty in girls and integrate the genetic, biologic, and environmental (e.g., products used at home, diet, lifestyle, and socioeconomic) factors that act together and independently to the onset of puberty. Approximately 1,400 girls are participating, with an average enrollment age of 7.1 and close to equal enrollment of Hispanic, Black, and non-Hispanic Caucasian girls, with a smaller number of Asians. Baseline pubertal maturation status revealed that 14 percent already have breast development, and environmental factors (dietary and chemicals) are hypothesized as the cause. Dr. Biro shared select research findings related to biomarker analyses, perfluorochemicals in serum, polybrominated diphenyl ethers (PBDE) levels, nutrient intake, and genetic susceptibility. Certain SNPs, for instance, are associated with both body mass index (BMI) and pubertal onset and are now being studied in the animal projects.

Biology Project—Dr. Sandra Haslam

Dr. Haslam said that the BCERCs' biology studies are focused on understanding normal mammary gland development, the effect of exposure on normal development, and assessment of risk based on susceptibility

after an exposure, with the intent of identifying underlying mechanisms and biomarkers of susceptibility and affected genes to prevent breast cancer. Investigations are using animal models to study endocrine disruptors, perfluorooctanoic acid (PFOA) exposure, diet, and radiation exposures, and collaborative microarray studies. Comparative studies in animals have identified new information on the mechanisms of steroid hormone action, particularly progesterone, and GATA-3 as a key regulator of pubertal development. A high level of PFOA, which was found in a subgroup of girls, is now positively associated with early pubertal maturation and a lower LDL cholesterol level. Diet studies currently show that most high-fat diets increase cell proliferation and mammary tumor susceptibility, including for subjects without obesity. Ionizing radiation alters the mammary gland tissue microenvironment and causes a deregulation of stem cell number. These effects are distinct from those on genomic integrity and have led to a paradigm shift from the theory that radiation works directly to damage deoxyribonucleic acid (DNA).

Community Outreach and Translation Projects—Ms. Janice Barlow

Ms. Barlow stated that the Community Outreach and Translation Cores (COTC) help ensure that the community voice is incorporated in BCERCs' activities, disseminate research, and evaluate community

involvement in the BCERCs. COTC collaborations with biology and epidemiology projects include community input on the selection and framing of research agendas, materials on environmental exposures, encouragement of co-authored scientific publications, and lay abstracts of scientific publications. Examples of these efforts include: the development of recruitment and retention tools and activities; an annual conference on early environmental exposures; and the dissemination of education and outreach materials. An evaluation of community involvement in BCERC found that community involvement increased community understanding and support of the scientific process, heightened sensitivity and propriety of the research, and improved communication and sharing of knowledge between scientists and community advocates.

In the discussion, the following points were made:

- The structure for following the existing cohort of 1,400 girls long term is under discussion.
- The BCERCs should conduct a longitudinal follow-up study on the PFOA exposure in the greater Cincinnati, OH area to determine whether the methodology used was effective in clarifying the facts.
- The CTOC should consider future interactions with communities as an opportunity to conduct research on communication strategies and information dissemination to the public.
- The BCERC Program was encouraged to educate families about the relationship between breast cancer, obesity, and exercise and determine the effect of this education.

VII. STATUS REPORT: COMMUNITY NETWORK PROGRAM (CNP)—DRS. LESLIE COOPER, CATHY D. MEADE, AND JUDITH S. KAUR

Introductions and Background of CNP—Dr. Leslie Cooper

Dr. Leslie Cooper, Program Director, Center to Reduce Cancer Health Disparities (CRCHD), informed the Board that the CNP engages members of racial/ethnic and underserved communities to better understand cancer and help identify strategies and research needed to reduce cancer health disparities in their communities, particularly with access, use of prevention interventions, and early detection of cancer. Dr. Cooper stated that the program is grounded in community-based participatory research (CBPR) for developing evidence based interventions, creating the next generation of disparities researchers, and expanding disparities research. CNP phases include capacity building and education (phase I), disparities research and training (phase II), and establishment of sustainability (phase III). Since the project's inception in 2005, more than 1,000 partnerships with community-based organizations have been formed. Efforts in sustainability began in 2008 and results include: publication of 518 peer-reviewed papers; input in policy changes for increased screening; increasing the number of trainees and researchers; and empowering the community in research. Dr. Cooper introduced the speakers: Drs. Cathy D. Meade, Moffitt Cancer Center and Judith S. Kaur, Mayo Clinic.

Community-Driven Research for Reducing Cancer Health Disparities—Dr. Cathy D. Meade

Dr. Meade described the importance of community involvement in reducing cancer health disparities and efforts of the Tampa Bay Community Cancer Network to bridge the discovery and delivery "disconnect" that is a key social determinant of the unequal burden of disease. The CNP provides a model for community engagement and encompasses education, outreach, service, and linkage components. Many Tampa Bay community partners indicated that most cancer information for patients and staff are received through the CNP, with topics covering breast, colorectal, and prostate cancers, as well as tobacco and nutrition. Specific examples of community-driven research in the Tampa Bay area include: 1) examining perceptions and behaviors about colorectal cancer in ethnic subgroups of U.S. Blacks; 2) barbers against prostate cancer; 3) cervical cancer beliefs in ethnic subgroups of Latina immigrants; and 4) a stress management tool kit for Latinas coping with chemotherapy. Impacting and reducing health disparities involves relevant methodologies, such as CBPR, to fit community members' cultural perspectives and situational realities, and

requires innovative approaches.

CNPs as Strong Clinical Trials Research Partners—Dr. Judith S. Kaur

Dr. Kaur reported on the clinical trials component of the CNP from her perspective as PI of the CNP's American Indian-Alaska Native Leadership Initiative. Indian communities refer to the initiative as "Spirit of Eagles," and in 2007, the Spirit of Eagles helped update and improve data for the NCI's "Annual Report to the Nation" regarding racial classification of American Indians. Special populations have been served successfully by the CNP and current members have developed infrastructure, sustainability, and momentum, as well as data sharing through peer-reviewed reports. In addition, public- and private-sector agencies and organizations have collaborated with CNP on reducing and eliminating cancer health disparities, such as the Lance Armstrong Foundation's work with Dr. Kaur's program to develop a strategic plan for American Indian and Alaska Native cancer survivors. Two examples of how CNPs are engaged in clinical trials research are: 1) the Walking Forward Program involving Phase II and III clinical trials, surveys, a patient navigator program, and analysis of Ataxia Telangiectasia mutated (ATM) gene; and 2) the Alaska Tobacco Research Program's Nicotine Exposure and Metabolism (NEAM) project which has enrolled 141 of 400 planned participants since its launch in August 2008.

In the discussion, the following point was made:

Many CNP sites have established collaborations with networks that include larger institutions, including with NCI comprehensive cancer centers, and other federal programs across the country.

VIII. UPDATE: TARGET PROGRAM—DRS. MALCOLM A. SMITH, STEPHEN HUNGER, AND JOHN MARIS

Introductions—Dr. Malcolm A. Smith

Dr. Malcolm A. Smith, Program Director, Cancer Therapy Evaluation Program, introduced the Therapeutically Applicable Research to Generate Effective Treatment (TARGET) initiative. Dr. Smith informed members that the initiative seeks to identify genes altered in childhood cancers that participate in cellular pathways relevant for cancer genesis and progression. These genes will serve as targets for developing diagnostic and prognostic tools and new therapies. Dr. Smith introduced the speakers: Drs. Stephen Hunger, Director, Center for Cancer Biologic Disorders, University of Colorado at Denver; and John Maris, Professor, University of Pennsylvania School of Medicine, and Director, Center for Childhood Cancer Research, Children's Hospital of Philadelphia.

Acute Lymphocytic Leukemia—Dr. Stephen Hunger

Dr. Hunger described work to identify genes involved in acute lymphocytic leukemia (ALL). The High Risk Childhood ALL TARGET initiative used a high risk patient population from a Children's Oncology Group (COG) clinical trial which have 5-year survival rates of only 62 percent. Sequencing DNA from these ALL patients identified a gene cluster that correlated with poor outcome. Further analyses found mutations in B-cell developmental pathway genes and IKAROS, a gene involved in lymphocyte development and homeostasis. Mutations in JAK2, a key signal transduction mediator, found to be mutated in myeloproliferative disorders and polycythemia vera (p. vera), were also seen. The mutant forms of JAK2 conferred growth factor independence and transformed cultured cells; factor-independent growth was inhibited by JAK inhibitor compounds. Patients with JAK mutations had an approximately 30 percent chance of not responding to current chemotherapy regimens, and children with combined JAK and IKAROS mutations had a 4-year relapse risk of 78 percent. These JAK mutations represent important targets for therapy and clinical agents that target JAK2, which are used to treat p.vera psuedokinase domain mutations, may be effective for treating ALL.

Neuroblastoma—Dr. John Maris

Dr. Maris described research to find new targets for neuroblastoma treatment. Two types of neuroblastoma exist; the more benign form of neuroblastoma is characterized by multiple copies of entire specific chromosomes, whereas the more aggressive forms are characterized by segmental aberrations, focal amplifications, and deletions. These can be further distinguished as very aggressive and less aggressive based on RNA copy number. As part of the TARGET initiative, a number of genes from neuroblastoma samples were sequenced, based on their location within regions of copy number aberration, differential gene expression, information from the literature, and if mutated in other cancers. This work has identified ALK, an oncogenickinase, which was previously shown to be involved in familial neuroblastoma and found by TARGET to be frequently amplified or mutated. Several of these mutations occur in the tyrosine kinase domain or extracellular domain and drive cell transformation and may be aberrant in 20-25% of patients. ALK serves as a good target for pharmacologic inhibition (although sensitivity depends on ALK mutation type), and work is ongoing to define the three-dimensional structure of ALK to improve efforts to find ALK inhibitors. A Phase I trial of an ALK inhibitor will begin within the next month.

In the discussion, the following points were made:

- Better genetic characterization of neuroblastoma will help identify children who need little to no cytotoxic therapy and help develop more precise therapies for children with high-risk disease.
- Future activities for TARGET will include next-generation sequencing, sequencing of the tyrosine kinome, and whole transcriptome sequencing. Targeted sequencing of specific genes, particularly those encoding tyrosine kinases, in additional patient cohorts also is planned.
- The TARGET initiative should consider developing screens for familial forms of neuroblastoma that occur later in life.

IX. SCIENTIFIC PROGRESS UPDATE: TRANSDISCIPLINARY RESEARCH ON ENERGETICS AND CANCER (TREC)—DRS. LINDA NEBELING, JOSEPH NADEAU, AND ANNE MCTIERNAN

Transdisciplinary Research on Energetics and Cancer—Dr. Linda Nebeling

Dr. Linda Nebeling, DCCPS, introduced the TREC initiative, which is a transdisciplinary program with the goals of understanding the mechanisms underlying the association between energy balance and carcinogenesis, developing effective approaches at the social-environmental and policy level for prevention and control of obesity, bringing together diverse disciplines, and creating new opportunities for transdisciplinary research. Obesity and overweight are increasing rapidly in the United States and account for between 10 and 20 percent of cancer-related deaths. TREC institutions include Case Western Reserve, University of Southern California, University of Minnesota, and Fred Hutchinson Cancer Research Center. Dr. Nebeling introduced the speakers: Drs. Joseph Nadeau, Chair, Department of Genetics, Case Western Research University; and Anne McTiernan, Fred Hutchinson Cancer Research Center.

Diet, Metabolism, and Cancers in Mouse Models—Dr. Joseph Nadeau

Dr. Nadeau described work to understand the relationship between diet, metabolic disease, and cancer using mouse models. He stated that cancer and metabolic disease both arise from complex interactions between inherited genetic factors and environmental factors such as diet and exercise. Two inbred mouse strains were used to investigate the interacting effects of genetics and diet on obesity and carcinogenesis. The A/J mouse strain remains lean on both high-fat and low-fat diets, whereas the C57 BL/6 strain becomes obese and develops liver disease and eventually hepatocellular carcinoma (HCC) on a high-fat diet. HCC is rapidly increasing in incidence and approximately 30 percent of these cancers are associated with obesity, diabetes,

and metabolic disease, rather than viruses or other traditional HCC risk factors. Switching the C57 BL/6 mice from a high-fat to a low-fat diet resulted in these mice becoming leaner and not developing liver disease or HCC. Interestingly, A/J mice exposed to the same environmental insult (high-fat diet) do not develop obesity or HCC, indicating an inherited genetic factor. This work shows that diet modification may help prevent liver cancer and that mechanisms for maintaining health exist in the presence of poor diet.

Energy Balance and Cancer: Carcinogenesis and Cancer Survival—Dr. Anne McTiernan

Dr. McTiernan described investigations of the relationship between dietary glycemic load and cancer. Rats fed a high glycemic index diet developed mammary tumors at an earlier age than rats fed a low glycemic index diet. The low glycemic diet favored reduced cell proliferation and a proapoptotic environment, leading to reduced carcinogenesis, whereas marker profiles reflected a procarcinogenic environment in animals fed high glycemic diets. TREC also has sponsored a study of overweight and obese breast cancer patients since these women have a poorer survival and increased risk of second cancers compared to slimmer patients. Analysis of markers in this multiethnic cohort of 550 women found that women with high levels of adiponectin (which is inversely associated with obesity) had the lowest risk of breast cancer death. Women with higher insulin resistance, which is more common in overweight or obese individuals, had an increased risk of breast cancer death.

In the discussion, the following point was made:

- Work is underway to test the effects of different types of dietary fats and sugars on carcinogenesis and also to understand the genetics of susceptibility or resistance to obesity and obesity-related cancers.

X. ADJOURNMENT—DR. ROBERT C. YOUNG

There being no further business, the 42nd regular meeting of the Board of Scientific Advisors was adjourned at 11:44 a.m. on Tuesday, 3 March 2009.