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

46th Meeting

BOARD OF SCIENTIFIC ADVISORS

Minutes of Meeting

June 28, 2010
Building 31C, Conference Room 10
Bethesda, Maryland

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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MINUTES OF MEETING
June 28, 2010

The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 46th meeting on Monday, 28 June 2010, 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 3:41 p.m. on 28 June for the NCI Director's report; a report on NCI Congressional relations; recognition of departing members; consideration of new and reissue requests for application (RFA) concepts presented by NCI Program staff; and reports on the Cancer Target Discovery and Development Network (CTD^2) and the Alliance of Glycobiologists.

BSA Board Members Present:

Dr. Richard L. Schilsky (Chair)
Dr. Paul M. Allen
Dr. Christine Ambrosone
Dr. Andrea Califano
Dr. Curt I. Civin
Dr. Susan J. Curry
Dr. William S. Dalton
Dr. Chi V. Dang
Dr. Robert B. Diasio
Dr. Jeffrey A. Drebin
Dr. Kathleen M. Foley
Dr. Todd R. Golub
Dr. James R. Heath
Dr. Mary J. C. Hendrix
Dr. Marc A. Kastner
Dr. Timothy J. Kinsella
Dr. Joshua LaBaer
Dr. Kathleen H. Mooney
Dr. James L. Omel
Dr. Stuart L. Schreiber
Dr. Bruce W. Stillman
Dr. Victor J. Strecher
Dr. Louise C. Strong
Dr. Frank M. Torti
Dr. Jean Y. J. Wang
Dr. James K. Willson

Board Members Absent:

Dr. Michael A. Caligiuri
Dr. Sanjiv S. Gambhir
Dr. Joe W. Gray
Mr. Don Listwin
Dr. Christopher J. Logothetis
Dr. Edith A. Perez
Dr. Robert D. Schreiber
Dr. Irving L. Weissman

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 46th 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 8 MARCH 2010 MEETING MINUTES - DR. RICHARD L. SCHILSKY

Motion: The minutes of the 8 March 2010 meeting were approved unanimously.

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

Dr. John Niederhuber, Director, NCI, welcomed members and provided information about the NCI fiscal year (FY) 2010 and 2011 budgets, planning for NCI's space needs for years ahead, NCI's vision for drug

development, and challenges ahead. Dr. Niederhuber said that the NCI appropriated budget trends reflect an upward movement following relatively flat budgets for several years prior to FY 2009. The FY 2009 ($4.97 billion (B)) and 2010 ($5.10 B) budgets included increases that were close to inflation rates; the American Recovery and Reinvestment Act (ARRA) funds to the NCI totaled $1.26 B in FY 2009-2010 and will continue to have an impact on FY 2011 and 2012 budgets. The FY 2011 President's Budget (PB) proposal for the NCI is $5.26 B, a 3.1 percent (%) increase over the FY 2010 operating budget.

Budget: Members were told that the NCI's FY 2010 budget portfolio remains stable: research project grants (RPGs) (44%); research centers (11%); other research (8%); research training (1%); research and development contracts (12%); intramural research (16%); and research management and support (8%). Competing RPGs are estimated to receive $496 million (M) in FY 2010, nearly $40 M more than projected, with a payline maintained at the 15th percentile. In addition, approximately $203 M has been set aside to fund RFAs, which is $70 M more than in FY 2009.

Infrastructure: Dr. Niederhuber informed members about the NCI's move in 2013 to the Shady Grove complex. The campus will include two custom-built, state-of-the-art buildings with 490,000 net square feet of usable space accommodating 2,400 staff members. The site was selected following a rigorous, year-long competitive bidding process conducted by the General Services Administration (GSA) in consultation with the NIH and NCI and space is available for future expansion. The location is close to the Shady Grove Adventist Hospital, Johns Hopkins University and University of Maryland facilities, and several pharmaceutical and biotechnology companies.

To meet the increasing need for public-private partnerships with biotechnology companies, NCI-Frederick is developing a 330,000 square foot Advanced Technology Research facility in Frederick, MD. The facility will contain NCI's Biopharmaceutical Development Program manufacturing facility, NCI's Advanced Technology Program, and administrative offices.

IOM Report: Dr. Niederhuber said that most drugs, particularly in oncology, fail in late stages of development. He noted that 70 % of cancer agents in Phase 2 fail to enter Phase 3, and 59 % that enter fail in Phase 3. The Institute of Medicine (IOM) report, *A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program*, has four goals, to: 1) promote consolidation and efficiency; 2) incorporate innovation in science and trial design; 3) provide adequate funding and support; and 4) incentivize participation by patients and physicians. Dr. Niederhuber stated that the clinical trials system must reflect the dramatic changes in cancer biology that have occurred during the past 20 years. The NCI's role is to assist the research community with difficult targets and to assume risks that the private sector might not take to advance the discovery of novel agents.

NExT: The accumulation of genomic disease characterization data and the sequencing of individual patients and their tumors will present challenges for storage, modeling, and analysis. The NCI Experimental Therapeutics (NExT) Program is a merger of NCI drug and imaging agent development programs, and will assist with the effort by advancing clinical practice and bringing improved therapies to cancer patients through support of the most promising new drug discovery and development projects. NExT includes the integration of the Pharmacodynamics (PD)-Biomarkers Program, the Chemical Biology Consortium (CBC), and the Functional Biology Consortium (FBC). The NExT application process involves four rounds of review annually; to date, three cycles have been completed. NExT plays an important role in developing agents for high-risk and other tumors that seek targets defined by cancer genomic and biologic studies and analyses of high-quality tissue samples. Patient characterization centers help to translate the data for use by practicing oncologists and thus improve diagnostics, disease management, and patient care.

In closing, Dr. Niederhuber reminded members that the NCI's Executive Committee (EC) Scientific Retreat in January 2010 discussed the Institute's investment in somatic genomic characterization of cancer, germline susceptibility, phenotypes, proteomics, and computational biology as an important means to translate knowledge from discovery to therapy. He said that participants agreed on several

principles that will underlie future advances, including that: cancer should be analyzed as a network of systems; multi-dimensional datasets will become standard; a new business model is needed for drug and diagnostic development in an age of personalized medicine; teamwork is critical for success; cancer is complex and heterogeneous; nanotechnology is driving revolutionary advances; and better incentives are needed for collaboration and tissue collection. Challenges to the NCI include forming successful public-private partnerships for drug development; updating the clinical trials system, and maintaining the momentum created by ARRA. Dr. Niederhuber expressed his appreciation to the Board, colleagues, and NCI staff for their support during his tenure as Director of the NCI.

In the discussion, the following points were made:

< Members agreed with the IOM Committee report concerning the need for change in the national clinical trials system, and supported the committee's position that all of its recommendations must be implemented to ensure the full impact of its report.

< The NCI has progressed significantly in attaining national accreditation for the Central Institution Review Board (CIRB). The CIRB has embraced the Operational Efficiency Working Group (OEWG) principles, resulting in reduction from an average 150 days to 36 days.

IV. NCI/CONGRESSIONAL RELATIONS - MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), informed members that the PB for FY 2011 was announced on 1 February, with $32.09 B for the NIH and $5.26 B for the NCI. House and Senate NIH budget hearings were held in April and May 2010. Ms. Erickson provided an update on NCI testimonies, upcoming hearings, and legislation of interest.

V. RECOGNITION OF DEPARTING MEMBERS - DRS. JOHN NIEDERHUBER AND RICHARD L. SCHILSKY

On behalf of the NCI, Drs. Niederhuber and Schilsky recognized the contributions of the five retiring BSA members: Drs. Susan J. Curry, Distinguished Professor and Dean, College of Public Health, The University of Iowa; William S. Dalton, CEO and Director, H. Lee Moffitt Cancer Center and Research Institute, University of South Florida; James R. Heath, Elizabeth W. Gilloon Professor and Professor of Chemistry, Division of Chemistry and Chemical Engineering, California Institute of Technology; Kathleen H. Mooney, Louis S. Peery, M.D., and Janet B. Peery Presidential Endowed Chair in Nursing Research Professor, University of Utah College of Nursing; and Robert D. Schreiber, Alumni Endowed Professor of Pathology and Immunology, Department of Pathology and Immunology, Washington University School of Medicine. Dr. Niederhuber acknowledged the importance of their contributions, both during and between BSA meetings, to the success of the Institute, and recognized the valuable volunteer hours that each donates to the NIH and the NCI.

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

Division of Cancer Control and Population Sciences Population-based Research Optimizing Screening Through Personalized Regimens (PROSPR) (RFA/Coop. Agr.)

Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences (DCCPS), told members that the PROSPR concept is a joint effort between the NCI and Centers for Disease Control and Prevention (CDC) to enhance and maximize the effectiveness of cancer screening and prevention services. Dr. Croyle stated that PROSPR would focus on the implementation and outcomes of cancer screening in communities, identifying barriers to optimal application of screening in practice, and investigating ways to overcome those barriers. The primary aims of PROSPR are to study: (1) the comparative effectiveness and outcomes of existing and emerging cancer screening processes for breast,

cervical, and colon cancers; and (2) the balance of benefits and harms of cancer screening across recognized cancer risk levels. A secondary aim of the project is to share data and conduct preliminary studies relevant to future innovative research to optimize the screening process. The concept draws on the experience of the Breast Cancer Surveillance Consortium (BCSC) in terms of evaluation of breast cancer screening technologies in clinical practice and anticipates adding project data elements to the BCSC Shared Data Resource. Potential themes of the project include: (1) development of strategies to estimate and communicate personalized risk, screening benefits, and harms; (2) mathematical modeling of the impact of screening improvements; and (3) organizational and behavioral interventions to address technical and/or human factors in screening. The PROSPR consortium will include up to five sites for the three disease sites, a statistical coordinating center, and a consulting panel. Dr. Croyle noted that this effort is timely and appropriate because comparative effectiveness research (CER) is a high priority for Congress. Ongoing multisite research initiatives do not address the entire screening process, and new screening technologies are emerging.

Subcommittee Review. Dr. Christine B. Ambrosone, Professor of Oncology, and Chair, Department of Epidemiology and Cancer Prevention and Control, Roswell Park Cancer Institute, expressed the Subcommittee's support for the concept, noting that definitive guidelines for cancer screening are needed. The Subcommittee requested clarification about PROSPR's proposed activities for breast cancer screening, given the success of the BCSC. Members were informed that the PROSPR concept is not limited to mammography and data collection; PROSPR is intended to create a platform and infrastructure to monitor implementation of new technologies. The Subcommittee suggested that the concept incorporate navigation and screening recruitment efforts, and recommended that the role of population sciences in the translational research continuum be made clearer in the concept. Members received clarification that most applications would focus on one cancer, since the screening for breast, cervical, and colon cancers is conducted in different physical locations. The Subcommittee also expressed concerns about the concept's generalizability, unless large health care providers participate, and the breadth of the concept from different screening tools to comparative effectiveness and studying gaps in diagnostics. NCI should consider requiring partnership with major health care providers and access to informatics systems to automate dissemination to clinical practice.

The first year cost is estimated at $13.5 M for up to 15 research centers and $1.5 million for 1 statistical coordinating center, with a total cost of $75 M for 5 years.

In the discussion, the following points were made:

< The principal incentive for participation by health care practitioners is access to information on the effectiveness of screening in their practices. The intent is to link with a CDC program on surveillance of colorectal, cervical, and breast cancers.

< The RFA concept provides an opportunity to both co-stratify the relationship according to established biomarkers and discover new biomarkers with the collection of specimens.

< Electronic medical records are not a requirement for participation since the intent is to capture the heterogeneity of the health care system.

Motion. A motion to concur on the DCCPS' RFA/Coop. Agr. entitled "Population-based Research Optimizing Screening Through Personalized Regimens (PROSPR)" was approved with 23 yeas, 3 nays, and no abstentions.

Division of Cancer Treatment and Diagnosis & Division of Cancer Biology
Center for Strategic Scientific Initiatives Advanced *In Vivo* Imaging To Understand Cancer Systems (RFA/Coop. Agr.)

In describing the concept for advanced *in vivo* imaging to improve the understanding of cancer systems,

Dr. James H. Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), told members that i*n vivo* imaging can provide knowledge of cancer systems and networks, from tracking living cells to informing clinical care, that will help develop safer, more effective therapies for cancer patients. Dr. Doroshow stated that non-invasive imaging and mathematical modeling of systems/network biology are being used more extensively throughout the cancer research community to validate concepts under investigation; examples include studies of the p53/Mdm2 network using real-time bioluminescent imaging, and the application of apoptosis imaging in cancer therapeutics.

Members were told that the concept aims to advance collaboration and team science in four areas: (1) technologies and methods to advance high-resolution intravital, *in vivo* microscopic imaging; (2) development and validation of cancer-specific *in vivo* probe and reporter systems; (3) integration of micro- and macroscopic data; and (4) development of new approaches of modeling, integrating, and visualizing multiscale imaging data. The goal of this RFA concept is to facilitate collaboration among investigators in the In Vivo Cellular and Molecular Imaging Centers (ICMICs) with investigators in the Integrative Cancer Biology Program (ICBP), Tumor Microenvironment Network (TMEN), Mouse Models of Human Cancer Consortium (MMHCC), and Centers of Cancer Nanotechnology Excellence (CCNE) to develop a new generation of imaging platforms that will reflect the biology beyond the cellular level that occurs in tissues, organs, and animals. Based on encouragement from reviewers, the concept requires applications to include investigators who are outside the groups specified above.

Subcommittee Review. Dr. Todd R. Golub, Director, Cancer Program, The Broad Institute of Massachusetts Institute of Technology and Harvard University, expressed the Subcommittee's overall support of the RFA concept with the added requirement for inclusion of a co-PI from the investigator community not already funded through one of the consortia named in the concept. The Subcommittee also recommended that the concept be revised to clarify the meaning of "*in vivo* advanced imaging" and to distinguish it from existing programs.

The first year cost is estimated at $5 M for 4-6 awards, with a total cost of $25 M for 5 years.

In the discussion, the following points were made:

< Concerns were expressed about possible justification for continuation of the collaborating centers based on participation by their investigators in this RFA concept. Staff noted that the NCI would not consider these collaborations as part of the justification for renewal.

< This concept presents "*in vivo* advanced imaging" as the means to extract data from an *in vivo* system, rather than an optical tool, such as positron emission tomography (PET) or computed tomography (CT).

< The research conducted under this RFA concept should include biologic systems research at the level of cells and tissues by noting the unique opportunities and needs for special imaging to further that science. Leveraging existing resources and requiring *in vivo* imaging technology development should be encouraged.

Motion. A motion to concur on the DCTD's RFA/Coop. Agr. entitled "Advanced *In Vivo* Imaging To Understand Cancer Systems" was approved unanimously with the amendment that the RFA/Coop. Agr. be released as an open competition with no requirements for inclusion of established networks.

Office of the Director
Comprehensive Partnership to Reduce Cancer Health Disparities (RFA/Coop. Agr.)

Subcommittee Review. Dr. Curry expressed the Subcommittee's enthusiasm for the concept reissuance, noting the program's many successes. The re-issuance is a limited competition RFA concept that would be open to established NCI-designated Cancer Center/minority-serving institution partnerships to advance

from planning (U56) to implementation (U54) grants. The last group of grantees with U56 planning grants is in the pipeline. The Subcommittee raised initial concerns about the conversion of the U54 mechanism from an RFA to a Program Announcement (PA), as PAs do not have dedicated funds. Staff clarified that NCI plans to maintain the U54 dedicated budget to fund future PA awards. An additional concern was that the limitation of awards to existing partnerships precludes opportunities for those not currently participating in this program. The Subcommittee was informed that an initiative for U56 planning grants will be reinstituted to allow new institutions into the pool. In the future, the PA for U54 grants would include a sunset clause to ensure that institutions that have received 10 years of U54 support would no longer be eligible to apply. When institutions compete for a 5-year renewal, the application must include a plan to phase in institutionalization to ensure sustainability.

The first year cost is estimated at $6.25 M for 4–5 U54 awards, with a total cost of $31.25 M for 5 years.

Motion. A motion to concur on the Office of the Director's RFA/Coop. Agr. entitled "Comprehensive Partnership To Reduce Cancer Health Disparities" was unanimously approved.

Division of Cancer Biology
NCI Tumor Microenvironment Network (TMEN) (RFA/Coop. Agr.)

Dr. Dinah Singer, Director, Division of Cancer Biology (DCB), informed members that the goals of the TMEN during 2006–2011 were to generate a comprehensive understanding of the composition of the normal stroma and the role of the stroma in tumor initiation, progression, and metastasis, as well as to develop reagents, resources, and infrastructure to advance understanding of the tumor microenvironment. Dr. Singer stated that scientific accomplishments included: 1) the identification of a characteristic invasive gene signature in tumor initiating cells which, when combined with a wound repair signature derived from other stromal cells, predicts relapse and survival; 2) development of new therapeutic approaches to circumvent the chemo- and radio-resistance of tumor initiating cells; and 3) elucidation of the mechanisms by which bone-marrow-derived cells influence tumor development and progression. TMEN has developed critical resources, including validated Engelbreth-Holm-Swarm (EHS) sarcoma matrix (Matrigel), stromal antibodies, and banks of tumor initiating and murine bone marrow cells.

The intent of the reissuance is to build on and expand TMEN's successes. Investigation of emerging novel concepts in the tumor microenvironment will require teams of interdisciplinary scientists to collaborate on large-scale, complex problems. The network structure will accelerate the development of new areas in tumor microenvironment research, encourage collaborations, facilitate the training of junior investigators, and develop new resources for the research community. New areas of scientific emphasis will include: stem cells, tumor dormancy and metastasis, metabolic dysregulation, cell fusion and exosome secretion, the microbiome, and gradients and flow of soluble factors. The proposed TMEN will solicit interdisciplinary teams, including disciplines not represented in the first phase, such as chemical and mechanical engineering.

Subcommittee Review. Dr. Curt I. Civin, Associate Dean for Research and Director, Center for Stem Cell Biology and Regenerative Medicine, University of Maryland School of Medicine, expressed the Subcommittee's strong support for the concept, especially the new areas of emphasis and the need for new teams and investigators. Additionally, the concept has the potential to provide significant insight into a complex area.

The first year cost is estimated at $9.054 M for 9 awards, with a total cost of $45.272 M for 5 years.

In the discussion, the following points were made:

< Consideration should be given to incorporating translational research in the concept, including the investigation of small molecules that act in the tumor microenvironment.

< The concept emphasizes the *ex vivo* use of human tumor samples and human cells to study the tumor microenvironment, including human tissue engineering.

< One of TMEN's unique contributions is the generation of resources for the community, which are made available after testing and widely publicized to the cancer research community.

Motion. A motion to concur on the DCB's RFA/Coop. Agr. entitled "NCI Tumor Microenvironment Network" was approved with 23 yeas, no nays, and 1 abstention.

Office of the Director (OD)
SBIR Phase II Bridge Awards to Accelerate the Development of Cancer Therapeutics, Imaging Technologies, Interventional Devices, Diagnostics, and Prognostics Toward Commercialization (RFA)

Subcommittee Review. Dr. Dalton expressed the Subcommittee's unanimous support for the reissuance. He noted the NCI Small Business Innovation Research (SBIR) Program's financial success and additional level of due diligence provided by the involvement of venture capital matching funding. Six projects awarded since 2009 received $17.5 M from the NCI and more than $50 M from private industry. The concept document was well written, and the Subcommittee applauded the study of metrics to determine whether the Bridge was accomplishing its original goals. The Subcommittee also considered whether the awarded projects might have found commercialization success without the Bridge and discussed increasing the ratio of venture capital funding to three-to-one.

The first year cost is estimated at $10 M for 5-10 R44 awards, with a total cost of $30 M for 3 years.

In the discussion, the following point was made:

< NCI's SBIR Program has been restructured and stands as an excellent model for other NIH institutes and government agencies. Commercialization is the best endpoint available to measure the effect of invested dollars.

< Staff should request more than one reissuance to minimize the need for annual Board review.

Motion. A motion to concur on the OD's RFA/Coop. Agr. entitled "SBIR Phase II Bridge Awards To Accelerate the Development of Cancer Therapeutics, Imaging Technologies, Interventional Devices, Diagnostics, and Prognostics Toward Commercialization (RFA)" was approved unanimously.

VII. THE CANCER TARGET DISCOVERY AND DEVELOPMENT NETWORK (CTD^2)—DRS. ANNA BARKER, STUART L. SCHREIBER, WILLIAM C. HAHN, AND ANDREA CALIFANO

Introduction—Dr. Anna Barker

Dr. Anna Barker, Deputy Director, stated that the five CTD^2 Network centers funded through Grand Opportunity (GO) grants are collaborating to systematically examine discoveries, models, and bioinformatics approaches that will be needed to propel cancer drug discovery forward. Dr. Barker introduced the speakers: Drs. Stuart L. Schreiber, Morris Loeb Professor, Harvard University, and Director, Chemical Biology Broad Institute of Harvard and MIT; William Hahn, Dana-Farber Cancer Institute; and Andrea Califano, Director, Center for the Multiscale Analysis of Genetic Networks, and Professor, Department of Biomedical Informatics, Institute of Cancer Genetics, Columbia University Medical Center.

Translating Genetic Patterns of Cancer to Drug Efficacies—Dr. Stuart L. Schreiber

In his overview of the CTD^2 Network, Dr. Schreiber stated that the aim is to bridge the gap between

cancer genomics and future cancer therapeutics. The overall goal is to relate the genetic features of cancers to acquired cancer dependency, acquired by specific somatic mutations that drive these cancers, and to identify small molecules that target the dependency. The CTD^2 Network is exploiting three major advances in the science of small molecules: (1) innovations in next generation synthetic chemistry that reach "undruggable" targets or processes; (2) innovations in cell culturing and the ability to examine cancer cells in the context of the tumor microenvironment; and (3) innovations in determining the targets and mechanisms-of-action of small molecule probes and drugs. Small molecule probe development of three members of the nuclear receptor SET domain-containing (NSD) family of histone methyl transferases, which have been associated with multiple myeloma are being investigated. The Network has identified a small molecule that targets the AHNAK-containing protein complex, and is investigating small-molecule probes of *ID-4*, an ovarian cancer oncogene, and *ID-1* for glioblastoma. Probes also are being developed that target reactive oxygen species (ROS) that are found at high levels in cancer cells.

The CTD^2 Network is also developing next-generation cancer cell line databases by annotating cell lines by their genetics. Investigators at the University of Texas Southwestern (UTSW) Medical Center are investigating several hundred genetically characterized lung cancer cell lines and have classified these into eight clades; they selected one cell line from each clade and are using these cell lines to perform detailed studies of RNAi and small molecules to find correlations between genotype and small molecule sensitivity. A probe kit is being developed by the CTD^2 Network involving the identification and synthesis (36%) of 225 compounds that have been characterized for their sensitivity to specific targets through genetic features. For example, a drug such as rapamycin would be included because there is a dominant drug resistant allele that eliminates response to rapamycin when introduced into cells, allowing one to know whether an effect is due to its interactions with the mammalian target of rapamycin (mTOR). From these investigations and also based on other hypotheses developed from CTD^2 Network research, probe kits are being developed. Recent results of pilot studies on these probe sets have identified promising patterns of sensitivity for a BCL2 antagonist and a very selective compound for HDAC6.

Functional Cancer Genomics—Dr. William C. Hahn

Dr. Hahn informed members that the CTD^2 Network and the centers are attempting to manipulate gene functions to link cancer genomics to cancer therapeutics. He noted that although the knowledge has to begin in genomics, there must be an understanding of the function of genes and gene networks to prioritize genes that are worthy of further study. Members were told that they are conducting systematic studies to address gene functions with four centers using RNAi based approaches in different tumors. The Dana Farber Cancer Institute group conducts loss-of-function and gain-of-function screens with genes that are identified by The Cancer Genome Atlas (TCGA), and then takes the promising genes into an *in vivo* context to determine if there was a context dependency of particular genetic alterations. This approach was applied to ovarian cancer cell lines and a small number of genes were identified that are both amplified in ovarian tumors or mutated and essential to the tumor, including *kRAS* and *ID-4*. An investigation of *ID-4* showed that *ID-4* transforms in the context of inactivated *MEK* allele; treatment with targeted nanoparticles to *ID-4* ablated ovarian tumors in animals and increased survival.

The Cold Spring Harbor Laboratory investigators are taking a complementary approach by constructing shRNA and cDNA libraries and screening for oncogenicity with a transplantable mouse model. Twenty novel tumor suppressor genes and oncogenes have already been discovered and validated. The UTSW group has identified major subtypes (clades) of non-small cell lung cancer through mRNA expression profiles. Chemical biology and genetic screens are searching for compounds that have specific sensitivity based on the clade representation or genes that seem to be required in particular clades versus other clades. A strength is the ability to share data among CTD^2 PIs and the broader scientific community.

From Oncopathway Addiction to Drug Discovery—Dr. Andrea Califano

Dr. Califano stated that the CTD^2 Network's biggest accomplishment is the ability to use hypotheses-generating approaches to understand the different targets, chemical modulators, mechanisms-of-action,

and biomarkers to determine whether the information is appropriate to translate to patients. In the context of therapeutics for cancer, the previous approach has been studying a spectrum of genetic alterations that occur in a small subset of the population. Dr. Califano noted that it is important that this is broadened to a larger population, which may be able to occur using a systems biology approach that relates to the ability to dissect specific regulatory modules. As an example, in the past, treatments for glioblastoma were stratified to different subgroups, those expressing proneural genes, mesenchymal genes, and proliferative disease. Another approach is to ask what regulates a tumor to further define specific signatures. An investigation of regulators identified five transcription factors associated with the regulatory logic of the cell. Two of the regulatory genes (i.e., transcription factors)—*C/EBP*, both *beta* and *delta*, and *Stat3*—appeared to be responsible for regulating all mesenchymal targets. These were validated in subsequent tests, which also showed that these factors work synergistically. In a study of 72 patients with glioma,100 % of those patients who were double positive for *Stat3* and *C/EBP beta* died within 120 weeks; approximately 50 % of those who were double negative for the two genes were alive at 120 weeks. Network based activity signatures may also be valuable in defining drug sensitivities and potential synergy of drugs.

In the discussion, the following points were made:

< The CTD^2 Network investigators should consider collaborating with the CBC where possible.

< A committee composed of CTD^2 Network PIs and individuals appointed within each center has been formed to define the standards both for data integration across the studies and with the broader scientific community.

< Consideration should be given to leveraging the Cancer Target Discovery and Development (CTD^2) Network to bioinformatics platforms, such as XenoBase, to better integrate basic science and drug discovery information with data from electronic health records.

VIII. ALLIANCE OF GLYCOBIOLOGISTS—DRS. MICHAEL PIERCE, AJIT VARKI, JAMES PAULSON, AND MICHAEL A. HOLLINGSWORTH

Dr. Peter Greenwald, Director, Division of Cancer Prevention (DCP), informed members that the Alliance's research relates to an important part of biology that involves nutritional science, chemistry, and proteomics. Dr. Greenwald introduced the speakers: Drs. Michael Pierce, Director, University of Georgia Cancer Center, Member, Complex Carbohydrate Research Center, University of Georgia, and Co-Chair of the Alliance of Glycobiologists for Detection of Cancer and Cancer Risk; Ajit Varki, Distinguished Professor of Medicine and Cellular and Molecular Medicine and Co-Director, Glycobiology Research and Training Center, University of California, San Diego; James Paulson, Professor, Departments of Chemical Physiology and Molecular Biology, The Scripps Research Institute; and Michael A. Hollingsworth, Professor, the Eppley Institute, Departments of Biochemistry and Molecular Biology, and Pathology and Microbiology, University of Nebraska Medical Center.

Introduction and Overview—Dr. Michael Pierce

Dr. Pierce explained that the mission of the Alliance is to investigate the aberrant expression of glycan structures on cell surfaces that occurs during oncogenesis to gain an understanding of cancer progression, with translational implications for diagnosis, prognosis, and response to therapy. The Alliance also serves as a conduit for other investigators to facilitate clinical validation of glycan biomarkers. He noted that Alliance funding began in 2007, with seven laboratories that use diverse glycotechnology platforms. Collaborations are developed within the Alliance and with other investigators, including the Consortium for Functional Glycomics (CFG), the National Center for Research Resources (NCRR), and the EDRN. The Alliance's web site provides details about its members, publications, and research programs and also serves as a repository for data generated by Alliance members.

Glycosylation Changes in Cancer—Dr. Ajit Varki

In an overview of glycobiology, Dr. Varki stated that every living cell is covered by a dense and complex array of glycans (sugar chains); specific alterations in these glycans occur in cancer. He also told members that glycoproteins, that is, proteins that contain glycans bonded to their amino acids, are already approved as biomarkers for some cancers. Glycan alterations in cancer cells include: increased branching of *N*-glycans; changes in the amount, linkage, and acetylation of sialic acids; *O*-glycan truncation; expression of immature *N*-glycans; altered expression of ABH(O) blood group-related structures; altered expression and enhanced shedding of glycosphingolipids; alterations in sulfation of glycosaminoglycans; and increased expression of hyaluronan. Several of these alterations currently are being investigated by Alliance researchers as potential targets for biomarker discovery. Effects on mucins also are prominent; alterations in the structure of glycans on the surfaces of epithelial cells lead to the secretion of mucins into the bloodstream in cancer. Cancer mucins mimic and interact with selectins; *in vitro* and *in vivo* evidence indicates that these mucins are involved in tumor progression and probably also in the altered blood clotting commonly observed in cancer.

Dr. Varki noted that his research focuses on sialic acids, which are located on the tips of various sugar chains in mammalian cells. There are two major types of sialic acids: Neu5Ac and Neu5Gc; humans lost the ability to make the latter during evolution but are exposed to it in their diet. Findings obtained using a novel sialoglycan array that detects Neu5Gc-specific antibodies suggest that immunologic reactions to Neu5Gc from animal sources may contribute to adverse human health effects. Exposure to dietary Neu5Gc generates Neu5Gc-sialyl Tn and antibodies against it. Incorporation of Neu5Gc into the epithelium of the prostate, colon, breast, and other organs in the presence of these antibodies may increase the risk of cancer. Future research directions include: the quantification of Neu5Gc in urine and antibodies to Neu5Gc in blood, with the aims of predicting cancer risk; developing new methods of early detection, prognosis, and monitoring; and finding a way to eliminate Neu5Gc from the body.

Glycomics Resources Funded by NIH—Dr. James Paulson

Dr. Paulson described glycomics resources funded by various NIH Institutes and Centers, which include the National Institute of General Medical Sciences (NIGMS)-funded Consortium for Functional Glycomics; the National Heart, Lung and Blood Institute (NHLBI)-funded Programs of Excellence in Glycoscience; and four centers funded by the NCRR; as well as the NCI-funded Alliance of Glycobiologists. Dr. Paulson explained that the goal of the NIGMS-funded Consortium for Functional Glycomics (CFG), which he leads, is to define paradigms by which glycan-binding proteins and glycan ligands mediate cell communication. The CFG developed the first usable high-throughput glycan microarray by developing a large library of compounds that have a common immune linker, which were printed on *N*-hydroxysuccinimide (NHS)-activated slides using standard robotic printing. This microarray has become a very successful tool for the glycomics community. It has been used in Alliance laboratories for the detection of: 1) anti-Neu5Gc antibodies and urinary Neu5Gc levels for the early diagnosis of cancer; 2) anti-glycan antibody-based signatures of several types of cancer, including non-small-cell lung cancer, mesothelioma, melanoma, and ovarian and breast cancers; identification of anti-glycan autoantibody signatures as prostate cancer markers; and 3) auto-antibodies to glycopeptide epitopes as early detection biomarkers for pancreatic cancer and adenocarcinomas.

Investigators and Scientific Areas—Dr. Michael A. Hollingsworth

Dr. Hollingsworth summarized the work of the seven laboratories in the Alliance, which involves application of state-of-the-art technologies to define unique glycan structures associated with cancer progression, as well as define antibody responses to unique oligosaccharides and glycopeptide epitopes during cancer progression. Three Alliance laboratories focus on the discovery of cancer-associated glycans, and four investigate antibody responses. The technologies used include: 1) glycotranscriptome analysis, which involves examination of the expression patterns of micro RNAs and of messenger RNAs that help to regulate glycosylation; 2) mass spectrometry analysis of glycans and glycoproteins; and 3)

glycan and glycoprotein arrays for detecting unique autoantibodies. Current research in targeted glycoproteomics involves exploiting glycan expression on specific glycoproteins to identify potential cancer biomarkers, including invasive ductal breast carcinoma markers, two of which have been verified in breast carcinoma tissue and serum. Different tissues and organs have been found to express different sets of mucins, and the expression of mucins has been shown to be different in tumors than in normal tissues, which suggests possible approaches to early detection. Another laboratory is examining differences in glycosylation of EGFR, which is heavily glycosylated and is known to be a cancer target. Using mass spectrometry techniques, the researchers found structural differences between the membrane-bound and soluble secreted forms of EGFR, a finding that has the potential development of anti-EGFR antibodies for clinical trials. Mass spectrometry techniques also have been used to detect serum glycans unique to specific stages of breast cancer. Alliance investigators interface with Specialized Programs of Research Excellence (SPOREs), program project grant (P01) investigators, EDRN, and CFG.

In the discussion, the following points were made:

< A higher prevalence of antibodies to carbohydrate structures is seen in patients with early cancer than in those with advanced disease. Patients with advanced cancer have so much circulating antigen as well as antigen expressed in the tumor that their antibody titers decrease as a result of the formation of immune complexes.

< The ordering of sugar moieties on carbohydrate molecules varies, unlike the template-driven ordering of amino acids in proteins. Despite this variation, certain patterns of glycosylation seem to be selected for in cancer, and unique cancer-associated antigens therefore can be identified.

< The glycobiology of the gastrointestinal (GI) tract may influence GI cancers. Variations in the carbohydrate structures in the GI tract can lead to substantial changes in the microflora, including *Helicobacter pylori*. Changes in glycosylation also can change the cytokine environment in the GI tract.

IX. ADJOURNMENT - DR. RICHARD L. SCHILSKY

There being no further business, the 46th regular meeting of the Board of Scientific Advisors was adjourned at 3:41 p.m. on Monday, 28 June 2010.

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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