Board of Scientific Advisors

Meeting Minutes

June 28-29, 2007

Building 31C, Conference Room 10
Bethesda, Maryland

Quick Links

Members

Agenda & Future Meetings

Meeting Minutes

BSA: Page 1

The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 37th meeting on Thursday, 28 June 2007, at 8:00 a.m. in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Robert C. Young, President, Fox Chase Cancer Center, presided as Chair.

The meeting was open to the public from 8:00 a.m. until 5:00 p.m. on 28 June for the NCI Director's report, report on NCI Congressional relations, presentation on the genetic basis of kidney cancer, recognition of departing members, final report of the Translational Research Working Group (TRWG), panel discussion of the Clinical Trials Working Group (CTWG) and the TRWG, and consideration of Request for Applications (RFA) reissuance concepts presented by NCI program staff. The meeting was open to the public from 8:00 a.m. on 29 June until adjournment at 11:20 a. m. for a mini-symposium on integrated human and mouse systems genetics, an update on cancer from a global perspective, and a final report of the NCI Best Practices for Biospecimen Resources.

Board Members Present:
Dr. Robert C. Young (Chair)
Dr. Hoda Anton-Culver
Dr. Kirby I. Bland
Dr. Susan J. Curry
Dr. H. Shelton Earp III
Dr. Kathleen M. Foley
Dr. Sanjiv S. Gambhir
Dr. Todd R. Golub
Dr. Joe W. Gray
Dr. James R. Heath
Dr. Mary J. Hendrix
Dr. Eric Hunter
Ms. Paula Kim
Dr. Michael P. Link
Dr. Kathleen H. Mooney
Dr. Mack Roach III
Dr. Richard L. Schilsky
Dr. Jean Y. J. Wang

Board Members Present:
Dr. James K. Willson
Dr. Ellen Sigal
Dr. Margaret Ruth Spitz

Board Members Absent:
Dr. Paul M. Allen
Dr. William S. Dalton
Dr. Raymond N. Dubois
Dr. Patricia A. Ganz
Dr. William N. Hait
Dr. Leland H. Hartwell
Dr. Leroy Hood
Dr. Hedvig Hricak
Dr. Christopher J. Logothetis
Dr. Lynn McCormick Matrisian
Dr. Edith A. Perez
Dr. Robert D. Schreiber
Dr. Jane Weeks

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

TABLE OF CONTENTS

I. Call to Order and Opening Remarks; Dr. Robert C. Young
II. Consideration of the 5-6 March 2007, Meeting Minutes; Dr. Robert C. Young
III. NCI Director's Report; Dr. John Niederhuber
IV. NCI/Congressional Relations; Ms. Susan Erickson
V. The Genetic Basis of Cancer of the Kidney; Dr. W. Marston Linehan
VI. Special Recognition of Departing Members; Drs. John Niederhuber and Robert C. Young
VII. Final Report: Translational Research Working Group (TRWG); Drs. John Niederhuber and Ernest Hawk
VIII. Clinical Trials Working Group (CTWG) and the TRWG Panel Discussion; Drs. James Doroshow, Sheila A. Prindiville, and Ernest Hawk
IX. RFA/Cooperative Agreements New Concepts; Presented by

NCI Program Staff
Biospecimen Research To Enable Molecular Medicine (RFP)
Division of Cancer Treatment and Diagnosis (DCTD)
AIDS and Cancer Specimen Resource (ACSR) (Coop. Agr.)
Cooperative Human Tissue Network (CHTN)
Division of Cancer Control and Population Sciences
Cooperative Family Registry for Epidemiologic Studies in Colon Cancer (C-CFR) (Coop. Agr.)

Office of the Director
Comprehensive Minority Institution/Cancer Center Partnership (MI/CCP) (Coop. Agr.)
Innovative Molecular Analysis Technologies (IMAT) Program (RFA)
Multidisciplinary Career Development Award (RFA)
Division of Cancer Treatment and Diagnosis
Network for Translational Research in Optical Imaging (NTROI) (Coop. Agr.)
Adult Brain Tumor Consortium (Coop. Agr.)

X. Mini-Symposium: Integrated Human and Mouse Systems Genetics; Drs. Dinah Singer, Cheryl Marks, Kent Hunter, David Threadgill, and Jason Moore
Overview; Dr. Cheryl Marks
Modeling Human Breast Cancer Metastasis Susceptibility in the Mouse; Dr. Kent Hunter
The Collaborative Cross: A Platform for Data Integration and Systems Genetics of Cancer; Dr. David Threadgill
Epistasis and Its Role in Cancer Complexity; Dr. Jason Moore

XI. Cancer from a Global Perspective; Dr. Joe Harford

XII. Final Report: NCI Best Practices for Biospecimen Resources; Drs. Anna Barker and Carolyn Compton

XIII. Ongoing and New Business; Dr. Robert C. Young

XIV. Adjournment; Dr. Robert C. Young

I. CALL TO ORDER AND OPENING REMARKS - Dr. Robert C. Young

Dr. Young called to order the 37th regular meeting of the BSA and welcomed members of the Board, NIH and NCI staff, guests, and members of the public. Dr. Young reminded Board members of the conflict-of-interest guidelines and confidentiality requirements. He called attention to confirmed meeting dates through November 2009. 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.

top

II. CONSIDERATION OF THE 13 MARCH 2006, MEETING MINUTES - Dr. Robert C. Young

Motion: The minutes of the 5-6 March 2007 meeting were approved unanimously.

top

III. NCI DIRECTOR'S REPORT - Dr. John Niederhuber

Dr. John Niederhuber, Director, NCI, welcomed members and stated that he would report on the status report for NCI's fiscal year (FY) 2007 appropriations, the FY 2008 legislation, the NCI's FY 2008 projected operating budget, the launch of the NCI Community Cancer Centers Program (NCCCP) Pilot, and the role of NCI in building partnerships across the scientific community

Status Report on Fiscal Year (FY) 2007 Appropriations. Dr. Niederhuber informed members that during the final quarter of FY 2007, Type 5 grants were at 2.9% below commitment of record per NIH policy; competing grants averaged $324K per NIH policy; approximately 20 percent of the competing pool was reserved for exceptions; the Special Programs of Research Excellence (SPOREs), Clinical Cooperative Group Program, and Cancer Training and Career Development remained at the FY 2006 levels, and the Cancer Centers Program increased 2 percent from FY 2006. Dr. Niederhuber noted that the NCI currently supports 63

Cancer Centers, including two new centers: Dan L. Duncan Cancer Center, Baylor College of Medicine, Dr. C. Kent Osborne, Director; and Stanford Comprehensive Cancer Center, Stanford School of Medicine, Dr. Irving Weissman, Director. The R01 payline for the end of the year is at the 15th percentile, and the *R01 payline is at the 21st percentile. The total portfolio of grants equals 5,175, and the FY 2007 success rate is estimated at 19 percent.

Status of Legislation for FY 2008. Members were told that the FY 2008 President's Budget (PB) request was $4.78B for FY 2008 and the Senate Appropriations Subcommittee recommended $4.91B. In its markup on 7 June of the FY 2008 Labor/Health and Human Services (HHS) Appropriations Bill, the House Appropriations Subcommittee on Labor, HHS, and Education recommended an appropriation of $29.7B to the NIH, which is $750M (or 2.6%) over the FY 2007 Joint Resolution (JR07) and $1.03B (or 3.6%) over the FY 2008 PB. It provides $4.87B to the NCI, which is an approximately $73M (or 1.5%) increase over FY 2007. These figures include the $63.2M that would have been programmed in past years for the NIH Roadmap Initiative or Common Fund. In a statement by Representative David Obey (D-WI), Subcommittee Chair, the increase recommended for the NIH was intended as an investment to: 1) increase the number of new and competing research grants by approximately 545 over FY 2007 to about 10,645; 2) lift the 2-year freeze on the average cost of new research grants; 3) help train the next generation of researchers; and 4) provide $110.9M for the National Children's Study and $300M for the global acquired immune deficiency syndrome (AIDS) fund.

The Senate full committee mark-up would appropriate $29.9B to the NIH, which is an increase of $1B (or 3.5%) over FY 2007 and $1.28B (or 4.5%) over the FY 2008 PB. It provides $4.91B to the NCI, which amounts to a $113M (or 2.3%) increase over FY 2007. Both House and Senate budgets include the $63.2M that would have been programmed in past years for the NIH Roadmap Initiative or Common Fund and now is a direct appropriation to the NIH Office of the Director (OD).

NCI FY 2008 Operating Budget Development. Dr. Niederhuber described mandated expense increases that must be considered in developing the FY 2008 operating budget based on the $4.91B recommended in the Senate Subcommittee markup for the NCI.

This would be an increase of $112.5M over the FY 2007 appropriation of $4.8B. An estimated $20M would be set aside in consideration of the potential for the NIH Director and DHHS Secretary to exercise their transfer authority, reducing the subtotal of available funds to $92.5M. NCI-wide requirements for estimated competing research project grant (RPG) increases, rent/lease/ utilities increases, a Small Business Program increase, and mandated salary increases could reduce the available subtotal to $26.1M. The NCI Director's Reserve set aside would reduce available new funds to $1.12M. The FY 2008 budget development challenge will be to identify revenue resources that cover increases in required expenses and to generate a pool of about $70 M for new initiatives that address emerging scientific opportunities, program expansions, and program restorations. In July, the EC will explore potential recoveries and redeployments to achieve that goal.

Members were told that the NCI budget will likely continue to be less than the inflation rate for the foreseeable future. Dr. Niederhuber outlined four needs that the NCI will work to address: 1) finding and funding the best science and the best scientists; 2) managing expectations; 3) leveraging additional resources; and 4) continuing scientific growth and maintaining a balance within the NCI portfolio.

Launch of NCI Community Cancer Centers Program (NCCCP) Pilot. Dr. Niederhuber reported that, earlier in the week, the NCI initiated the NCCCP, a pilot program aimed to make improvements across the continuum of cancer care, from risk assessment to treatment and care delivery. NCI staff have worked diligently on this effort starting in FY 2006, and the initial NCCCP meeting was attended by approximately 100 cancer physicians and administrators from community hospitals who previously had not felt a strong connection with the NCI community.

Role of the NCI in Building Partnerships. To better address cancer, a disease of staggering complexity, Dr. Niederhuber said that the NCI has developed a number of programs, centers, and networks, including the Integrated Cancer Biology Program, the Center for Human Cancer Genetics, and the Network-Centric Biomedicine. The Institute sees opportunities to work with many partners through a "team science" approach in a number of areas in the cancer research arena, such as sub-cellular imaging, protein capture, physics, and technology development. In addition to

supporting the extramural community, the NCI is facilitating the building of bridges among industry, academia, and the public sector through several activities, including the Advanced Technology Partnership Initiative, the NCCCP, the NIH Clinical Research Center, and NCI's drug discovery and development resource. In these efforts, the NCI views treatment as managing a network, not just a pathway, which is important in the progression toward individualized medicine.

In addition, Dr. Niederhuber discussed the importance of the Life Sciences Consortium, which includes a significant number of representatives from the private sector through a 501[c]3 structure. Its initial goals are to: 1) develop a common language for contracting; 2) work on intellectual property issues; and 3) address issues of antitrust.

In discussion, the following points were made:

The current emphasis on inter and cross disciplinary research in planning for future scientific endeavors is to be commended; however, the NCI in planning for future budgets does not yet appear to be addressing the need for more investment in translation of the discoveries to the population.

- In terms of budgetary concerns, the NCI should consider a strategy to express the opportunities lost and numbers of grants and programs not funded, particularly as these impact the NCI's leadership role in biomedical research and the recruitment and retention of young investigators.
- The NCI Director is encouraged to write an article for Science and other journals aimed at young investigators and the impact of a flat budget and grant support.

top

IV. NCI/CONGRESSIONAL RELATIONS - Ms. Susan Erickson

FY 2008 Appropriations. Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), reviewed the appropriations process leading to the enactment of the FY 2008

budget.

New Legislation. Ms. Erickson reported on recently introduced legislation of interest to the NCI, including: 1) The National Cancer Act; 2) Comprehensive Cancer Care Improvement Act; 3) Cancer Screening, Treatment, and Survivorship Act; 4) Breast Cancer Stamp; and 5) several bills focused on screening/coverage related to specific cancers.

Congressional Activities. Ms. Erickson reported on visits to the NIH and NCI by congressional members and their staff: 1) April 12, Representative Dave Weldon (R-FL), a member of the Labor/ HHS Committee, was given an extensive tour of the Center for Cancer Research (CCR), in particular, the pediatric unit, where he was introduced to patients participating in clinical trials of new therapies; 2) May 31, a staff member in the office of Representative Brian Higgins (D-NY) visited the NIH to learn about the NCI intramural program; 3) Senator Barbara Mikulski (D-MD) conducted an informal hearing on 24 May to discuss the decline in mammography rates. Ten of the 16 female Senators attended. Presentations were given by Dr. Niederhuber; Dr. Nancy Greene, Division of Cancer Control and Population Sciences (DCCPS); and representatives from the American Cancer Society (ACS) and Susan G. Komen Foundation; and Dr. Douglas Lowy, CCR, NCI, presented information on cervical cancer vaccines to the Congressional Biomedical Research Caucus on 20 June.

Members were informed that they would be contacted for feedback on services provided by the OGCR, i.e., legislative update written report included in the meeting materials, presentations at the Board meetings, and staff responsiveness to requests from members for information.

In discussion, the following point were made:

- Outreach materials sent to Congress should be instructive, stimulate dialogue, and help ensure that cancer remains a high priority. Additionally, interested parties can remain updated on legislative issues related to cancer by visiting NCI’s public policy Web pages.
- OGCR should send members additional legislative and reference materials regarding lung cancer screening as well

as report to BSA on specific bills that have significant relevance to cancer.

top

V. THE GENETIC BASIS OF CANCER OF THE KIDNEY - DR. W. MARSTON LINEHAN

Dr. W. Marston Linehan, Chief, Urologic Surgery, NCI, presented information about NCI's investment in understanding the genetic basis of cancer of the kidney. Kidney cancer incidence has been rapidly increasing each year since tracking began in 1972. In 2007, approximately 51,000 Americans will be diagnosed with kidney cancer and 14,000 will die, making kidney cancer the sixth leading cause of cancer death. If the cancer is localized, surgery can result in a 95 percent 5-10 year survival rate; if the disease is advanced, only 18 percent of patients will survive for 2 years.

Attempts to identify genes involved in kidney cancer began in the early 1980s. This task was complicated by the number of different histologic types of cancer that occur in this organ, each with different clinical courses and responses to therapies. Early work showed that there was consistent loss of a segment of chromosome 3 in tumors found in patients with sporadic, non-inherited kidney cancer. To help determine which genes in this regions were involved in kidney cancer, the mapping of genes involved in hereditary forms of kidney cancer was begun, based on the theory that these genes also would be involved in sporadic kidney cancer.

The hereditary kidney cancer program that was established at the NIH has collected samples from families with kidney cancer to perform linkage analysis and physical mapping to identify kidney cancer genes. More than 100 individuals from 26 laboratories and branches within seven Institutes and Centers (ICs) at the NIH have participated in this program.

As part of this research effort, four types of inherited kidney cancer were identified: 1) clear cell, 2) Type 1 papillary, 3) Type 2 papillary, and 4) chromophobe. The most well-known type of inherited kidney cancer is Von Hippel Lindau (VHL). VHL is an inherited cancer syndrome that places carriers at risk for

developing tumors in a number of different locations, including the kidneys. Historically, 35 to 45 percent of VHL patients died of metastatic kidney cancer if the disease was not detected and managed early. Initially, open surgery (partial nephrectomy) was performed to manage this cancer, but by the middle of the 1990s, laparoscopic surgery has been used to remove tumors, and patients managed in this fashion have not developed advanced disease.

Analysis of clinical material and tumors from NIH's kidney cancer program confirmed the consistent loss of a region on the short arm of chromosome 3 in sporadic and hereditary kidney cancer. The VHL gene, which was identified in 1993, is composed of three axons, and mutations in the gene have been observed in the germ lines of 338 families. Mutations in this gene are observed only in cases of clear cell kidney cancer, not in Type 1 or Type 2 papillary cancers or chromophobe oncocytoma. The VHL gene also was determined to be a classic tumor suppressor.

Isolation of the VHL protein and associated proteins found that VHL functioned as an E3 ubiquitin ligase. Analysis of the structure of the VHL protein found that the alpha domain binds elongin C and the beta domain binds hypoxia-inducible factor (HIF) for ubiquitin-mediated degradation. HIF is a transcription factor that promotes the transcription of a number of genes, including vascular endothelial growth factor (VEGF) and transforming growth factor alpha (TGF-a). VHL functions by binding HIF1 and 2 through its oxygen-dependent domain (ODD) and promoting their degradation through the ubiquitin-mediated degradation pathway. Mutations in the ODD results in over-accumulation of HIF1 and the activation of VEGF, erythropoietin1 (EPO1), and other downstream genes, but not in tumorigenesis. Instead, HIF2 appears to be critical for the development of kidney cancer.

The identification of pathways and downstream genes relevant to the development of clear cell kidney cancer has contributed to strategies for the development of therapeutic agents. Treatment with the VEGF antibody bevacizumab has been associated with a statistically significant difference in progression-free survival. Sunitinib, which targets VEGF and the platelet-derived growth factor receptor (PDGF-R) results in a significant increase in disease-free progression (31% response rate) compared to interferon. Sorafenib, which also targets VEGF and PDGFR, is associated with a 10 percent response rate and an increase in disease-free

progression. A new approach for kidney cancer targets the mTOR pathway with the drug temsirolimus; this should affect HIF transcription and looks promising for patients with clear cell kidney cancer and poor prognosis. Treatment with temsirolimus resulted in a 10 percent response rate and a statistically significant increase in survival compared with interferon.

Other approaches include analyzing the activity of genes upstream of the VHL-HIF interaction. A small molecule that targets and inhibits transcription of HIF1 has been identified, and screening for small molecules that target HIF2 transcription is underway. HIF also has been found to form a tight bond with the molecular chaperone, heat shock protein (Hsp) 90, which contributes significantly to HIF stability. In a preclinical model, VHL-clear cell kidney cancer cells were treated with geldanamycin, which disrupted HIF-Hsp90 binding and resulted in the degradation of HIF1. A clinical trial of geldanamycin in VHL patients has begun.

Similar work has identified genetic bases for other types of kidney cancer. Hereditary papillary renal carcinoma, described in 1994, is an autosomal dominant form of inherited kidney cancer with nearly 100 percent penetrance. The same type of therapeutic approach used for VHL patients, including surgical management, is used for these patients. Analysis of families carrying this form of inherited kidney cancer identified the causative gene as the proto-oncogene MET, which is the receptor for hepatocyte growth factor (HGF). Activating mutations in the tyrosine kinase domain of the receptor are found in families positive for this form of inherited kidney cancer; thus, MET functions as a classic oncogene. The identification of this gene has permitted diagnosis of the condition. A trial is currently in progress to test a multi-kinase inhibitor for the treatment of hereditary papillary carcinoma. Antibodies to HGF itself and to its receptor also are being tested.

Another ligand for MET is folliculin where, mutations cause Birt-Hogg-Dubé (BHD) syndrome, a hereditary cancer syndrome. Patients develop skin lesions, lung cysts, and chromophobe kidney cancer. Folliculin functions as a tumor suppressor gene and frameshift mutations are observed in BHD patients. Inhibiting the phosphorylation of folliculin dramatically improves the survival of BHD patients.

In discussion, the following point were made:

- Large-scale genome sequencing currently in progress will add to the data previously gathered through genetic association studies. For example, approximately 60 percent of sporadic kidney cancers are now believed to have a hereditary component. Whole genome single-nucleotide polymorphism (SNP) assessment is in progress to find susceptibility genes for kidney cancer.

top

VI. SPECIAL RECOGNITION OF DEPARTING MEMBERS - DRS. JOHN NIEDERHUBER AND ROBERT C. YOUNG

Drs. Niederhuber and Young recognized the retiring BSA members Drs. Raymond DuBois, Shelton Earp, Patricia Ganz, Hedvig Hricak, Eric Hunter, Michael Link, Lynn Matrisian, Mack Roach, Margaret Spitz, and Ms. Paula Kim. Those members in attendance, Drs. Earp, Hunter, Link, Roach, Spitz and Ms. Kim, were presented the NCI Director's Service Award for their service on the BSA. Dr. Niederhuber acknowledged the importance of each retiring member's contributions, both during and between BSA meetings, to the success of the Institute, and he recognized the valuable volunteer hours that each donates to the NIH and the NCI.

top

VII. FINAL REPORT: TRANSLATIONAL RESEARCH WORKING GROUP (TRWG) - DRS. JOHN NIEDERHUBER AND ERNEST HAWK

Dr. Ernest T. Hawk, Director, Office of Centers, Training and Resources (OCTR), reminded Members that the charge to the TRWG was to evaluate the status of NCI's investment in translational research and to provide input on its future direction in an inclusive, representative, and transparent manner. Dr. Hawk stated that the TRWG focused on basic, Phase 1, and Phase 2 trials to make use of advances in the knowledge of cancer biology and living systems, respond to the global environment, and take

advantage of opportunities while operating under a flat budget.

TRWG activities resulted from the review of the Clinical Trials Working Group (CTWG) report and other foundational documents; the development of a Web-based communication plan; organization of two roundtables for public input, and analysis of NCI's current investments in translational research. The TRWG defined translational research as transforming scientific discoveries arising in the laboratory, clinic, or population into new clinical tools and applications that reduce cancer incidence, morbidity, and mortality. Six developmental pathways to clinical goals including biospecimen-based and image-based risk assessment pathways and intervention pathways for agents, immune reponse modifers, intervention devices, and lifestyle alterations were drafted. The focus was on early translation and examined risk assessment and interventions as two pathways to achieve clinical goals to ensure that the most promising concepts entered the developmental pathways and advanced to the clinic or to "productive failure." The NCI's translational research funding in FY 2004 was estimated at $1.3B, or 30 percent of NCI's budget.

Members were told that the TRWG summary vision was to build a collaborative and multi-disciplinary enterprise, which is tailored to early translational research, providing an essential link from discovery to patient and public benefit. The key objectives include: improving coordination and collaboration and instilling a culture of goal-oriented management; improving the identification of the early translation research opportunities; to tailor existing and new funding programs to facilitate translation progress and promote researcher participation; and enhancing the efficiency and effectiveness for individual projects and many supporting activities. The Report described TRWG initiatives that fell under three common themes: coordinated management, tailored funding programs, and operational effectiveness. Specifically,

> **Coordinated Management:**1) establish a coordinated NCI-wide organizational approach to manage the diverse early translation portfolio, reduce fragmentation and redundancy, and ensure that resources were focused on promising opportunities; 2) designate a specific portion of the NCI's budget for early translational research; 3) develop a set of award codes to accurately capture the early translational research portfolio; and 4) create a prioritization process to

identify the most promising research opportunities based on scientific quality, feasibility, and expected clinical or public health impact.

Tailored Funding Program: 1) modify guidelines for multiproject, early translational research awards and improve processes and mechanisms for the review and funding of investigator-initiated early translational research; 2) establish Special Translational Research Acceleration Project (STRAP) awards to advance a select number of especially promising early translational research opportunities; 3) establish a program for joint NCI/industry funding of collaborative early translational research projects integrating the complementary strengths of all parties; and 4) more effectively and efficiently provide access to the translational research services.

Operational Effectiveness: 1) build a project-management system involving staff both at the NCI and at extramural institutions to facilitate coordination, communication, and management of milestone-based progress for multidisciplinary, early translational research projects; 2) coordinate essential core services to reduce duplication and ensure high-quality services for projects and investigators; 3) improve standardization, quality control, and accessibility of annotated biospecimen repositories and their associated analytic methods; 4) improve negotiation of intellectual property agreements and agent access; 5) increase NCI interaction and collaboration with foundations and advocacy groups; and 6) strengthen training programs and career incentives to maintain an early translational research workforce.

Four principles were identified to guide the timeline and budget: 1) organizational and administrative initiatives should be initiated as soon as possible; 2) a prioritization process must be in place before STRAPs can commence; 3) the administrative budget should be kept to a minimum by leveraging existing structures; and 4) the recommended extramural funding program is expected to require less than 1 percent of the NCI budget.

Dr. Hawk stated that plans are to publish the pathways to clinical goals, develop translational research award codes based on these

pathways, implement a communications plan for the TRWG report, and convene an internal working group to discuss implementation strategies. In conclusion, he acknowledged the work of the co-chairs, Drs. Lynn Matrisian, Vanderbilt-Ingram Comprehensive Cancer Center, and William Nelson, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University.

In discussion, the following points were made:

- The Foundation for the NIH (FNIH) should be leveraged for additional resources for translational research. A number of foundations have expressed notable interest in the STRAP Program.
- NCI's portfolio likely encompasses more than 35 percent of the translational research, as young and seasoned investigators now design their research with translation in mind.
- The NCI is encouraged to perform a cost-savings assessment, including incentives for use of shared core resources that would allow any savings to be used to assist younger researchers.

top

VIII. CLINICAL TRIALS WORKING GROUP (CTWG) AND THE TRWG PANEL DISCUSSION — DRS. JAMES DOROSHOW, SHEILA A. PRINDIVILLE, AND ERNEST HAWK

Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), informed members that approaches used to integrate the work of the CTWG and TRWG and reduce duplication between the two groups were: 1) expansion of the Clinical Trials Advisory Committee (CTAC) scope to include early translational research; 2) modeling the Translational Research Operations Committee (TROC) on the Clinical Trials Operations Committee (CTOC) to provide a dedicated focus and agenda across the NCI for early translational research; 3) establishing within the Coordinating Center for Clinical Trials (CCCT) the Translational Research Support Office (TRSO); 4) coordinating revision of program guidelines (Cancer Center, SPOREs, and Cooperative

Groups) to promoted collaboration and ensured consistency and efficiency in CTWG/TRWG implementation; 5) coordinating implementation of model templates for standard clinical trials contract clauses, intellectual property, and material transfer; and 6) coordinating outreach to patients and physicians for clinical trial participation, tissue donation, and imaging archiving.

top

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

Biospecimen Research To Enable Molecular Medicine (RFP)

Dr. Carolyn Compton, Director, Office of Biorepositories and Biospecimen Research (OBBR), described the new Biospecimen Research for Molecular Medicine initiative. Biospecimens represent an essential element in translational research, and their careful collection, processing, banking, and distribution to researchers are important steps in finding new diagnostic and therapeutic approaches to the patient. Using a systematic, comprehensive approach to improve biospecimen quality for research and clinical medicine, the NCI has developed two state-of-the-science guidances for biobanking: the NCI Best Practices for Biospecimen Resources and the Biospecimen Resource Evaluation Tool (BRET).

Because high-throughput, multiplex approaches to analyze biospecimens depend on high-quality human biospecimens, the NCI has developed a strategic partnership with the College of American Pathologists (CAP) whereby the CAP has agreed to receive any new NCI data to produce CAP standard operating procedures (SOPs), which then can be implemented through its laboratory accreditation program.

Proposed Approach to Extramural Research. The NCI is seeking an ordered approach to fill in knowledge gaps through a request for proposal (RFP) mechanism and a sole-source contract that will approach pre-acquisition and post-acquisition phases of

the life cycle of the biospecimen. The pre-acquisition variables will be studied through a sole-source contract with the post-acquisition variables analyzed through the RFP mechanism. A central molecular analysis laboratory will do all of the analyses through another contract mechanism with the Frederick Cancer Research and Development Center (FCRDC). Additionally, a broad agency announcement (BAA) will be used to solicit creative solutions to unmet needs and difficult issues.

RFP: Research Studies in Cancer and Normal Tissue Pre-Analytical Variables. The intent of the RFP is to define the influence of individual acquisition and post-acquisition variables on quality-controlled downstream molecular analysis. Plans are to collect well-annotated differentially processed and preserved cancer and normal tissues under highly defined protocols, performing molecular analysis on defined platforms in a central laboratory under strict quality assurance and quality control (QA/QC), and conducting iterative experiments to define variables in specimen acquisition processing and storage. It is anticipated that this effort will result in a large collection of samples produced under defined conditions with specific variables built in to the specimen collection. The RFP mechanism provides the ability to: generate a collection of very high quality specimens with built in known variables for molecular analysis comparisons; specify how the specimens are annotated, collected, processed, stored and shipped; stipulate that molecular analysis data be made publicly available as soon as it is produced; create a pipeline of molecular analysis data through the NCI's relationship with the CAP; and provide incentives for applicants who are able to link to and use the molecular data produced in the central laboratory as added value for their own research. The structure of the project is expected to involve between two and four large hospital centers that have high-volume surgery. In Years 1 and 2, there likely will be an opportunity to study the variation within a center and across centers; Years 3 through 5 would involve the systematic alteration of selected variables with intraspecimen comparisons.

Sole Source Contract: Intra-operative Variables. The RFP is to determine the effects of anesthesia, other surgical drugs, and intra-operative ischemia time on gene expression and protein analysis. A company that is unique in its ability to collect detailed datasets on intraoperative events in the operating room and bank all tissues according to a strict protocol that is replicatable in every case has

been identified. Plans are to sample primary rectal cancer and normal rectal mucosa, and metastatic colorectal cancer and normal liver, before (at diagnostic endoscopy) and during surgery at prescribed intervals, as well as collect detailed pre- and intra-operative data. The selected vendor has unique capabilities in surgical control, rigorous tissue SOPs, highly trained staff, full range of protocols for clinical and surgical data collection, and dedicated surgeons.

BAA: Research and Development on Human Biospecimen Quality. To engage the extramural community in helping define and address the most important biospecimen challenges, the BAA mechanism will allow the solicitation of innovative solutions and approaches to issues related to the quality control variables in biospecimens. Contract proposals will be invited for the development of specimen-specific, platform-appropriate systems for human biospecimen QA and quality management. The contract mechanisms will allow the NCI to maintain control over the research process while engaging the private sector. Areas of interest for proposals include: 1) effects of anesthesia, analgesics, or chemotherapy on downstream proteomics analysis of plasma and serum by mass spectrometry; 2) effects of robotic versus open surgery on prostate and colon cancer biospecimen quality and molecular profiles; and 3) methods and systems to determine whether biospecimen quality is sufficient for specific types of molecular analysis. Dr. Compton informed members that the expected outcomes are: 1) publications and presentations on the effect of human specimen pre- and post-acquisition variables on downstream molecular analysis; 2) publications from members of the scientific community at large in response to the raised awareness of the importance of such studies; 3) increased attention to QA/QC important to downstream molecular analysis by manufacturers of consumables, reagents, and robotics; 4) CAP guidelines based on new data with implementation in the clinical arena; 5) implementation of data-driven standards for specimen handling in new venues; and 6) greater reproducibility of research and clinical results.

The RFP’s estimated total cost is $12M for 3-4 awards to be issued once a year for the initial 2 years of a 5-year program. The BAA mechanism is estimated to cost $7.5M total and will be issued once a year for 5 years. The 2 year one time issuance sole source contract is for $1M in total cost.

Subcommittee Review. Dr. Michael Link, Lydia J. Lee Professor of Pediatrics and Chief, Division of Hematology, Oncology, Stanford University School of Medicine, informed members that the subcommittee had requested clarification about several aspects of the program, and that the questions had been answered by the presentation. Dr. Link noted that the subcommittee was concerned about the number of variables for any procedure and the need for consistency and speed in performing biopsies. Members were told that while the funding mechanisms (RFP, sole source contract, and BAA) were deemed appropriate, the subcommittee expressed concern about the non-competitive nature of the sole source contract, as well as the possibility of developing too narrow a scope for the BAA. As far as the BAA, the NCI was encouraged to obtain further input from the broader scientific community as to the real problems that need a solution. Dr. Link said that the subcommittee felt this work is necessary to achieve progress and concurred with reissuance.

In the discussion, the following point was made:

- The challenge remains concerning how the compiled information will be used, especially in terms of the control of variables and attribution of results when a multitude of variables are present.

Motion:A motion to concur with the Request for Proposal (RFP) entitled “Biospecimen Research to Enable Molecular Medicine” was approved with two abstentions.

The Biospecimen Resource Evaluation Tool (BRET)

Dr. Compton described the BRET, which provides a consistent, comprehensive, and transparent framework for evaluating the quality of resources that would be useful and could be applied to each of the resources coming forward. The BRET consists of two components: a key characteristics table and a master evaluation checklist. The key characteristics table provides a schema for classifying the biospecimen resource by type and then determining its relevance by mapping the type to each of the criteria on the master checklist. The master evaluation checklist, which consists of a comprehensive compendium of all of the quality indicators for all types of biospecimen resources, focuses on performance and

effectiveness.

Dr. Compton informed members that the BRET tool was launched as a pilot to the ongoing Colon Cancer Family Registry (C-CFR), AIDS and Cancer Specimen Resource (ACSR), and CHTN programs. The approach to implementation includes applying it to all biospecimens resources coming forward to the EC and BSA, publishing the BRET prior to use, and developing a quality improvement program for biospecimen resources that the OBBR will oversee.

top

Division of Cancer Treatment and Diagnosis

AIDS and Cancer Specimen Resource (ACSR) (Coop. Agr.)

Subcommittee Review. Dr. Eric Hunter told members that the ACSR serves as a unique resource for biological specimens, as it provides longitudinal samples for studies to examine the changing nature of the human immunodeficiency virus (HIV) epidemic. The biorepository is organized into three regional sites: George Washington University, Ohio State University, and UCSF. Central operations and the data coordinating center are located at UCSF. The biorepository was assessed using the BRET approach, and it received a strong performance rating with more than 60,000 samples distributed at the time of the review to 68 researchers. The subcommittee indicated that it is a unique resource in that there are pre- and post-highly active anti-retroviral therapy (HAART) and international collections. Members were told that it also has significantly impacted the development of diagnostics and therapeutics, particularly Kaposi's sarcoma. They noted that OBBR recommended improvements, i.e., more stringent standard operating procedures (SOPs), had incorporated into the concept. Dr. Hunter noted that the requested funding level is consistent with NCI's FY 2007 budget for a biorepository of cancer samples from HIV-infected individuals, and with the Office of AIDS Research (OAR) FY 2008 plan. The Subcommittee endorsed the reissuance, but noted that the future of repositories, including the possibility of a central repository, will eventually need to be addressed.

The first year cost is estimated at $3.6M for 4 U01 awards and a total cost of $18 M over 5 years.

In the discussion, the following points were made:

- Tracking publications resulting from use of this repository was difficult. The OBBR recommendation to establish a better system to track publications should be pursued.

Motion: A motion to concur with the reissuance of the DCTD's Cooperative Agreement entitled "AIDS and Cancer Specimen Resource" was approved with three abstentions.

top

Cooperative Human Tissue Network (CHTN) (Coop. Agr.)

Subcommittee Review. Dr. Shelton Earp, Director, UNC Lineberger Comprehensive Cancer Center, commended the materials that the subcommittee received was a model of how RFA concepts should be written. Dr. Earp noted that approximately 300,000 specimens have been collected and distributed through the CHTN during the last 5 years, which is prospective and investigator-initiated, rather than focused on just collecting tissue. The network has developed a good system for tracking publications that includes impact factors and a citation index of the top articles that have been published; in total, 850 publications have resulted from the CHTN. The network investigators are pathologists who, as a group, have been involved in educational efforts and the development of SOPs They have played an important role in collecting pediatric tissues; 90 percent of the pediatric banked tissues are attributable to CHTN efforts. The Subcommittee raised concerns about limiting the competition to the existing award holders via a Letter RFA rather than an open competition. Staff noted that a limited competition would reduce significant disruptions to the analytical work that has occurred. All six sites were currently performing well and likely will continue to do so. Dr. Earp stated that the subcommittee was satisfied with the CHTN scientific contributions and supported re-issuance.

The first year estimated cost is $5.8M for 6 U01 awards and estimated total cost of $29M over 5 years.

In the discussion, the following points were made:

- Consideration should be given to mandating that investigators use the CHTN-provided identifier when they make their data publicly available. This would allow different investigators to identify whether they are publishing research on the same CHTN specimens as other investigators.
- The CHTN has developed priorities to guide its consideration of requests for specimens and does require Institutional Review Board (IRB) approval.

Motion: A motion to concur with the reissuance of the DCTD's RFA/Cooperative Agreement entitled "Cooperative Human Tissue Network" was approved unanimously.

top

Division of Cancer Control and Population Sciences (DCCPS)

Cooperative Family Registry for Epidemiologic Studies in Colon Cancer (C-CFR) (Coop. Agr.)

Drs. Robert Croyle, Director, DCCPS, and Daniella Seminara, Program Director, CFR, DCCPS, reminded members that nearly 13,000 families have been recruited into the C-CFR, which includes the largest collection of African American and Japanese American familial colon cancer syndrome families. Goals for this re-issuance (Phase III of the C-CFR initiative) include: understanding the etiological, molecular, heterogeneity of colon cancer; assessing and modifying the effect of genetic and environmental factors; and developing guidelines for personalized medicine and prevention. Whereas Phases I and II of the initiative focused on the recruitment process, Phase III emphasizes molecular characterization and data access including digital images and pathology data. New enrollment will target adding gene carriers and other high risk families, provide a greater depth of clinical

data, and focus on the greater centralization of biospecimen management.

With the exception of the behavioral core which has been discontinued, the current RFA concept requests, at a reduced budget and duration, support for the maintenance of remaining cores for the existing C-CFR sites. Future plans include: 1) an RFP contract to support a centralized “split” biospecimen repositor;, and 2) a Program Announcement (PA) to solicit applications using the C-CFR infrastructure, as the OBBR recommended. The PA is expected to maximize the use of the C-CFR, ensure that applications are examined in a scientifically prioritized manner according to peer review, and ensure the wise use of the biospecimen resource. Regarding the biospecimen repository, plans are to implement a centralized biorepository and to work closely with the OBBR, C-CFR sites, and the biorepository contractor to ensure integration into the overall NCI biospecimen strategic plan.

Subcommittee Review. Dr. Kathleen M. Foley, Attending Neurologist, Pain and Palliative Care Service, Department of Neurology, Memorial Sloan-Kettering Cancer Center, informed members that the OBBR’s review and constructive suggestions helped strengthen the program. The C-CFR met the goals it identified, increased the followup of participants, performed molecular characterization, and increased the enrollment of African Americans and Japanese Americans. The presentation helped clarify the Subcommittee’s confusion about the PA. One Subcommittee member suggested that the NCI should consider the U24 mechanism, rather than U01, as it would broaden the program’s reach and identify C-CFR as a resource to the community. The subcommittee concurred with re-issuance.

The first year cost is estimated at $8M for 6 U01 awards and an estimated total cost of $32M (Biorespository) over 4 years and a BAA at $6.7M for the CFR component.

In the discussion, the following points were made:

- The registry conducts a systematic molecular characterization of known cancer susceptibility genes with the objective of adding this data to the central database. Adding specimen annotations to the registry, from

individual investigators' results, would require expanded resources.

- Regarding investigators who are not part of the network who request access to the data and specimens, the success rate (85%) is approximately the same as investigators within the network.
- The infrastructure for behavior research exists within the registry and R01 investigator initiated studies using registry resources should be encouraged.

Motion: A motion to concur with the reissuance of the DCCPS' RFA/Cooperative Agreement entitled "Cooperative Family Registry for Epidemiologic Studies in Colon Cancer" was unanimously approved.

top

Office of the Director

Comprehensive Minority Institution/Cancer Center Partnership (MI/CCP) (Coop. Agr.)

Subcommittee Review. Dr. Hoda Anton-Culver, Professor and Chief, Epidemiology Division, Department of Medicine, University of California-Irvine, reminded members that the Comprehensive Minority Institution/Cancer Center Partnership (MI/CCP) is awarded as a U54 mechanism and provides competitive grant funding for minority investigators, increases the competitive resource capacity for minority serving institutions, increases cancer outreach from cancer centers in minority communities, and helps ensure that more cancer center research is directed toward health disparities in their respective communities. Even though the program has been very successful, the subcommittee requested clarification about the numbers of minority investigators and students, their performance in the centers, data to indicate the number of trainees and the grantees, and the types of grants. Dr. Anton-Culver stated that staff provided clarification for all of their concerns, with good documentation. She noted that this concept would allow for new institutions to become involved. The subcommittee recommended concurrence with the re-issuance.

The estimated first year cost is $7.5M for 3 U54 awards and a total cost of $37.5M over 5 years.

Motion: A motion to concur with the reissuance of the OD's RFA/ Cooperative Agreement entitled "Comprehensive Minority Institution/Cancer Center Partnership" was approved with six abstentions.

top

Innovative Molecular Analysis Technologies (IMAT) Program (RFA)

Dr. Carolyn Compton, Acting Director, Office of Technology and Industrial Relations, OD, reminded members that the objective of the Innovative Molecular Analysis Technologies (IMAT) Program is to develop and apply new technologies that transform researchers' abilities to identify molecular changes that distinguish cancer and pre-cancer cells from normal cells. Its goals are to: 1) focus innovative technology development on cancer; 2) solicit highly innovative technology development projects from the scientific and medical communities; and 3) accelerate the maturation of meritorious technologies through to commercialization. Dr. Compton noted that the IMAT Program is unique in that it 1) focuses on the development of high-risk, high-impact, and high-payoff technology, and quantitatively addresses measures such as specificity, sensitivity, and speed; 2) is designed as a staged process that requires quantitative evidence of progress or feasibility before advancement to the next stage; and 3) links to small business funding opportunities (approximately one-quarter of applications and one-third of awards are targeted for business commercialization).

The IMAT Program has been organized such that a technology developer could enter during Phase I (or later) and follow the Program all the way through to commercialization. The R21 exploratory pilot phase requires no preliminary data; quantitative milestones established by the developer would be used as rating criteria. Phase II uses the R33 mechanism and requires feasibility data; the developer must plan for the development of the

technology and provide a description of the completed milestones of technology feasibility. Progress can be made to commercialization via the Small Business Innovation Research (SBIR) or Small Business Technology Transfer Program (STTR) programs.

Successes. Dr. Compton shared examples of successful IMAT grantees and their technologies. She stated that the IMAT Program has achieved a number of milestones regarding patents (58 in progress and 9 secured), licensing (27 in process and 19 secured), new companies (5 in progress and 7 started), partnerships (2 in progress and 38 formed), and technological commercialization (7 in process). More than 100 inventions with patents or patent applications have been based on IMAT awards.

Programmatic Changes. Dr. Compton said that the RFA concept included several changes in the IMAT Program. Specifically, the: 1) SBIR and STTR portions of the program will be managed administratively through NCI's new SBIR Development Center; 2) central administration of the sample preparation domain will be assigned to the OBBR; 3) receipt dates will be reduced from 3 to 2 per year; and, 4) RFA solicitations will be strengthened by expanding the scope to include areas in proteomics, nanotechnology, and epigenomics.

The request for refunding of the IMAT Program is to maintain the current funding levels: $3M per year for each of the innovative and emerging technologies domains, and $1M per year for the cancer sample preparation domain. The first year cost is estimated at $10.5M for approximately 50 (R21, R33, R21/R33, & SBIR/ STTR) awards/year and an estimated total cost of $52.5M over 5 years.

Subcommittee Review. Dr. Kirby I. Bland, Deputy Director, University of Alabama-Birmingham Comprehensive Cancer Center, University of Alabama School of Medicine, informed members that the subcommittee posed several questions to the NCI IMAT Program staff and that Dr. Compton's presentation addressed many of them. Dr. Bland informed members that the questions focused on: 1) whether or not the IMAT Program should be continued; 2) details of the budget; and 3) programmatic structural changes in relation to the small business technology program. Drs. Michael Weingarten, Director, SBIR Development

Center and Niederhuber indicated that the SBIR program's administrative and management functions had been centralized within the Institute and that staff with the appropriate expertise will oversee the work. Two other Institutes will be joining the NCI's efforts in the new SBIR Development Center. Dr. Compton confirmed that this concept recommends elimination of the R21/ R33 grant mechanism and a reduction in the number of receipt dates.

In discussion, the following points were made:

- The NCI should consider extending the length of the R21 grant from two to three years or continue the R21/R33 mechanism to allow less disruption and sufficient time to achieve.

Motion:A motion to concur with the reissuance of the OD's RFA entitled "Innovative Molecular Analysis Technologies Program" was unanimously approved but with suggestions to extend R21 grants to 3 years and not link R21 and R33 grants.

top

Multidisciplinary Career Development Award (RFA)

Subcommittee Review. Dr. James R. Heath, Elizabeth W. Gilloon Professor and Professor of Chemistry,

Division of Chemistry and Chemical Engineering, California Institute of Technology, informed members that this award funds postdoctoral fellows who conduct research in nanotechnology. The goal has been to encourage scientists trained in the physical sciences to receive training in cancer biology so that they will build and incorporate combination programs into their academic institutions. The program currently funds fewer than 10 people and is expected to increase during the next several years to around 20. The subcommittee noted that this type of fellowship is extraordinarily difficult to obtain from other funding agencies, and it endorsed the reissuance of the concept.

The first year cost is estimated at $750K for 11 (10 F32s; 1 F33) awards and an estimated total cost of $225M over 5 years.

Motion: A motion to concur with the reissuance of the OD's RFA entitled "Multidisciplinary Career Development Award" was approved unanimously.

top

Division of Cancer Treatment and Diagnosis

Network for Translational Research in Optical Imaging (NTROI) (Coop. Agr.)

Dr. Laurence Clarke, Chief, Imaging Technology Development Branch, Cancer Imaging Program (CIP), DCTD, indicated that the intent of the NTROI is to establish a multi-institutional network of teams to identify approaches to validate and translate optical methods for cancer detection, diagnosis, drug response, and image-guided interventions. Dr. Clarke stated that the clinical challenge is to integrate molecular imaging methods into advanced imaging platforms. Optical techniques were selected because they have the potential for imaging across resolution scales from the cellular to the organ level with molecular specificity. He noted that this is a highly leveraged research effort that has funded four multi-site teams, involves collaborations with many other investigators and more than 30 industry partners, and integrates the physical and molecular sciences. Interagency collaboration occurs with the FDA and the National Institute of Standards & Technology (NIST), which is considering the development of standards for biomedical imaging.

Dr. Clarke informed members that a NTROI workshop was held in October 2006 to evaluate progress. NTROI strengths included the evaluation of a leading-edge device technology using single and multi-site validation studies, promotes the sharing of prototype systems and molecular probes to target the same organ system, and contains a well organized network. Suggestions for improvement were to become more focused on optical methods being investigated and offer greater incentives to expand inter-team

collaboration.

The goals of the re-issuance are to: 1) further multi-modality imaging as a molecular imaging platform to add optical to other mature technologies; 2) facilitate functional-molecular imaging across different resolution scales from the cellular to the organ level; 3) improve methods that combine diagnosis with intervention; and 4) facilitate advanced methods for drug discovery and image-guided delivery. The NTROI planned deliverables include the: 1) development of partnerships with industry for commercial system access and expanded research collaboration; 2) sharing of resources for physical, pre-clinical, and pilot clinical validation studies; 3) development of integrated clinical decision tools where the clinical performance is evaluated in a standardized manner; and 4) transfer of combined technologies for targeted or organ-specific clinical applications into the clinical trial setting, which have potential for FDA approval.

The requested annual budget is approximately $1.2M per year for four teams/U54 awards for a estimated total of $24M over 5 years.

Subcommittee Review. Dr. Mack Roach, Chair and Professor, Department of Radiation Oncology, UCSF, stated that the NTROI had been productive, with more than 160 publications and approximately 30 clinical trials. Dr. Roach noted that the Program will need to address the conflicting issues of remaining focused on a few research areas, as suggested by the interim review experts, while continuing to expand the number of the investigators with whom the Program interfaces and integration of other types of imaging modalities with optical imaging. Dr. Roach stated that the subcommittee thought the Program had been successful in validating optical imaging technologies and are accessible for clinical evaluation. The Subcommittee recommended concurrence.

In discussion, the following points were made:

- Data should be collected to help determine when a combination modality is more appropriate to use than a single modality, particularly as applied to the population level.
- An open competition was chosen because integrating optical imaging with other imaging modalities may require new

partners or teams.

- The NTROI is interacting with the American College of Radiology Imaging Network (ACRIN) in that a new committee of ACRIN is looking at emerging technologies and includes NTROI members; and NTROI optical procedures are being proposed to ACRIN for inclusion in a clinical trial study.

- The NTROI should consider including members from the community or advocacy representatives in its deliberations.

Motion: A motion to concur with the reissuance of the Division of Cancer Treatment and Diagnosis' (DCTD) Cooperative Agreement entitled "Network for Translational Research in Optical Imaging (NTROI)" was approved with three abstentions, and with the suggestion that input should be obtained from the advocacy community.

top

Adult Brain Tumor Consortium (Coop. Agr.)

Subcommittee Review. Dr. Foley informed members that the concept limits the re-competition to a single consolidated consortium for which the leadership of the two existing consortia that have performed clinical trials in brain tumors could apply; the current members of the two groups will be required to compete for the 15 membership slots. The focus is to streamline the infrastructure to better prioritize studies and establish methodological resources. The subcommittee was told that the proposal had four reviewers who had asked questions and concurred with the recompetition, strongly supporting the need for the development of effective therapies to treat primary brain tumors, including through Phase I and II trials, the development of better pharmacokinetic/pharmacodynamic (PKPD) mechanisms, and an emphasis on translational research. The subcommittee's concerns about the flat budget and inconsistencies in the reporting on the number of patients that have been recruited were addressed. An additional issue was whether this research could be funded through other mechanisms, such as SPOREs or P01 grants; it was

noted that the two consortia comprise all the leading institutions and investigators in the country conducting clinical research in brain tumors. The subcommittee recommended concurrence.

The estimated first year cost is at $3.53M for 1 U01 award and a total cost of $18.1M over 5 years.

In discussion, the following points were made:

- With the consolidation of the two consortia, it is expected they will likely submit one application as one consolidated group.

Motion: A motion to concur with the reissuance of DCTD's RFA/ Cooperative Agreement entitled "Adult Brain Tumor Consortium" was approved unanimously.

top

X. MINI-SYMPOSIUM: INTEGRATED HUMAN AND MOUSE SYSTEMS GENETICS—DRS. DINAH SINGER, CHERYL MARKS, KENT HUNTER, DAVID THREADGILL, AND JASON MOORE

Dr. Dinah Singer, Director, Division of Cancer Biology (DCB), defined systems genetics as a new emerging field that combines classical mouse genetics, mouse modeling, and molecular epidemiology. Dr. Singer told members that the mini-symposium would provide an update on the field, describe NCI's contributions to the research, and outline future opportunities. She introduced the presenters: Drs. Cheryl Marks, Program Director, NCI-Mouse Models of Human Cancers Consortium (MMHCC); Kent Hunter, Laboratory of Population Genetics, CCR, NCI; David Threadgill, Department of Genetics, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill; and Jason Moore, Frank Lane Research Scholar in Computational Genetics, Dartmouth-Hitchcock Medical Center.

Overview. Dr. Marks informed members that it is important to develop relationships and multidisciplinary teams to address issues related to cancer susceptibility using a systems genetics approach.

The juxtaposition of research using mouse models against the cancer biology continuum and cross species comparisons with humans suggests that investigations using these models can have an effect on translational research.

When the initial RFA for the MMHCC was developed, it was believed that modeling cancers in mouse models would require modification of the germline of the laboratory mouse. However, it became apparent that the genetics of inbred mouse strains could be used to inform research on cancer susceptibility and resistance, and to study other factors such as response to therapy and the genetics of tumor biology. Dr. Marks stated that Dr. David Threadgill's presentation would describe ways in which systems genetics tools are integrated across human and model organisms to enable identification of the underlying factors, both intrinsic and extrinsic, that contribute to cancer susceptibility and resistance.

Modeling Human Breast Cancer Metastasis Susceptibility in the Mouse. Dr. Hunter's laboratory is described metastasis and how gremline polymorphisms affect the process of metastasis and gene expression signatures. A line of transgenic mice carrying the mouse PyMT antigen driven by a mammary-specific enhancer and promoter, used to investigate the effects of polymorphisms, were crossed to a large number of different mouse strains to examine the effect of different genetic backgrounds on metastasis. Comparing the maternal genotype of the mouse to which the PyMT animals were bred showed that metastatic index differed for the different strains, indicating that polymorphisms in the genetic background of the different strains of mice changed the metastatic phenotype. The results also suggested that many genes likely are associated with the change in phenotype, indicating that this is not a simple Mendelian trait.

A number of complex trait mapping experiments were performed to identify the regions of the genome that contained the genes responsible for the metastatic phenotypes. The proximal region of chromosome 19 showed associations with metastases suppression, and was narrowed down the gene SIPA1, which encodes a RAP1 GTPase. This work suggests that minor variations in the function of SIPA1, rather than loss or complete inactivation of the protein, have significant affects on metastasis in this mouse model.

Epidemiology studies were performed to determine whether

polymorphisms in human SIPA1 were associated with markers of poor prognosis in humans. Three SNPs in human SIPA1 were identified, including putative promoter polymorphisms that were significantly associated with the presence or absence of tumor cells in the lymph nodes of breast cancer patients. Comparison of the RNAi knockdown cell line with controls using Affymetrix arrays and Ingenuity Pathways analysis showed that SIPA1 is involved in controlling expression of a number of collagen and extracellular matrix genes. Previous work has shown that tumors can be categorized as metastatic or non-metastatic based on extracellular matrix gene expression patterns, suggesting that extracellular matrix is either an important causative component of metastasis susceptibility or a marker thereof, and could be used as an intermediate phenotype to find additional relevant genes.

A number of recombinant inbred panels were used to map phenotypic modifiers of metastasis. To complement this work, array experiments were performed to find regions of the genome that control the expression levels of the extracellular matrix genes. This work identified three regions that were reproducibly associated with expression of the extracellular matrix genes on chromosomes 7, 17, and 18. Dr. Hunter ‘s laboratory focused on analyzing the unannotated Riken gene, now named Anakin, located on chromosome 17. This gene appears to have a significant role in metastases susceptibility. Anakin was found to be highly associated with genes whose expression levels are positively associated with extracellular matrix gene expression, based on genome-wide correlation studies. Two-hybrid studies also found that Anakin associated with SIPA1.

Analysis of Anakin in humans found a variant allele (Pro435Leu substitution) that, when homozygous, is associated with lack of metastasis; one analysis found that none of the 300 patients homozygous for this variant developed distant metastasis. Comparing gene expression profiles from cells that ectopically express Anakin to control cell lines resulted in a gene expression profile that was analyzed and converted into human probe sets. The probe sets were analyzed on different breast cancer gene expression cohorts in an attempt to cluster patients into those that appear to over-express Anakin, based on the profile and those that do not and then determining if the difference in gene expression was associated with survival differences based on Kaplan-Meier curves. In three of four patient cohorts, overexpression of Anakin was

associated with improved survival. Anakin thus has an important role in metastasis susceptibility in both humans and mice.

Dr. Hunter stated that the research demonstrates that inherited polymorphisms can significantly impact tumor progression and metastasis in the mouse and human. These polymorphisms may function by altering extracellular matrix composition, and may also be an important component of prognostic gene expression profiles.

In discussion, the following points were raised:

- SIPA1 and Anakin are expressed in all tissues. Although maternal transmission of mitochondrial DNA should be considered, breeding was conducted only in one direction.
- The gene expression signatures work are not informative for lung and kidney cancer, because the metastasis suppressor genes show tissue-restricted expression. There is some evidence that the signatures may be informative for prostate cancer.
- Given the association of Anakin expression with ER/PR status, the polymorphism could be associated with a predisposition for either basal or luminal subtype breast tumors but no significant association with either of these subtypes has been found.
- A gene expression signature that integrates all information on relevant polymorphisms and that is detectable in normal tissues could be used in large-scale epidemiologic studies to predict metastatic potential.
- The Clinical Trials Cooperative Groups have collections of germline DNA that could be used to validate potential metastasis polymorphism signatures. Consider linkage of NCI's Systems Genetics Program with CTCG to facilitate the sharing of germline DNA collections.

Dr. Threadgill explained that the integration of the molecular aspects of specific disease processes with genetic and environmental information will help understand disease progression as well as an individual's susceptibility to developing disease such as cancer. A systems approach to genetic variation will help identify the key and critical components of biological networks that are associated with diseases and will help identify patients with a high probability of developing cancer and permit intervention at an early stage in the process. The creation of a

biomolecular map of mammalian variation that includes genetic variation at the DNA sequence level and at the phenotypic level, but also events occurring between these two points, will be critically important for understanding how environments alter gene activities.

Currently, it is difficult to integrate different types of biological data. A common platform to truly integrate and understand how the biomolecular space is altered by environmental exposures is needed. To build a new platform on which to perform quantitative analyses of limited genomes, a multiparental recombinant inbred mouse panel (Collaborative Cross) was developed; use of multiple parent strains rather than the usual two will encompass the variation present in the entire species. The panel permits analysis of any type of biological or environmental perturbation on a defined, common genetic architecture. Using this panel, data can be integrated across laboratories and over time, which determination of ever more precise predictive values defining disease course in any particular individual. The eight parental strains were chosen based on their ability to breed and by pre-sequence analyses that determined that these strains represented a level of genetic diversity analogous to the diversity observed in the human population.

The result of the breeding scheme was creation of a large fixed population. Different measurements can be taken and results incorporated into the common genetic architecture to begin mathematically building descriptors of what drives biological variation and how this variation translates into different disease susceptibilities. To address concerns that the mice are inbred in contrast to humans, pair-wise F1 matings will generate a population that represents 1 million unique genomes, or a large outbred population in which each individual has a unique genome. The power of this system lies in the ability to randomly perturb entire components of variation all at once rather than perturbing individual components one at a time and measuring their activities individually. Sequencing data was used to show that the collaborative cross captured approximately 90 percent of all the variation present in the mouse genome.

This resource will permit annotation of the genome with functional units and DNA sequence variance in biomolecular space, which will show how variation in the genome alters the intermediate biomolecular space, i.e., transcriptional profiles, metabolic

changes, or other processes. It also will permit understanding of how the biomolecular space is altered with respect to disease susceptibility. For example, cancer and obesity may have common links in some individuals, but the unique nodes within networks that drive this association will vary depending on the individual. Detailed maps of the biomolecular space will allow predictions of which alleles are important for which individuals and predictions of the disease likelihood or course in any one individual. This work will help develop an understanding of how each individual responds differently to different types of environmental perturbations.

In discussion, the following points were raised:

- The Collaborative Cross resource should be thought of as an epidemiological population. For example, assuming eight unique alleles associated with each gene, in a population of 1,000 individuals, the alleles would be queried 125 times over.
- Transgene or knockout alleles from inbred strains can be bred into the Collaborative Cross (through a series of F1 matings) and analyzed, if the characteristic of interest is dominant.
- The Collaborative Cross resource will be seeded with important phenotypes, such as baseline expression differences. Once this has been accomplished, individuals will be able to make use of previously collected data.
- The Collaborative Cross mouse populations will be housed in three central repositories (Israel, Australia, and Tennessee). Postdoctoral students would be sent to the central repositories to perform interventions of interest and collect data, with the bulk of the work being computational analyses.

Epistasis and Its Role in Cancer Complexity. Dr. Moore informed members that many genes and environmental factors contribute to the development of cancer and interact in complex ways to determine an individual's progress toward cancer. Interactions among biomolecules, environmental factors, transcriptional networks, protein-protein interaction networks, and tissues must be considered to fully understand tumor biology.

Epistasis traditionally refers to gene-gene interactions that lead to

deviations from simple Mendelian inheritance patterns. Biological epistasis refers to the physical interactions of biomolecules in a system, while statistical epistasis refers to deviations from a linear model summarizing the variation of DNA sequence information and phenotypes in a population. Current approaches for identifying genetic or environmental risk factors for different types of cancer analyze one risk factor at a time. Unfortunately, this approach is unlikely to identify most relevant risk factors. Different tumors will have different genetic and environmental etiologies, and tools are needed for studying complex interactions and heterogeneity.

A number of computational and statistical methods for detecting epistasis and gene-environment interactions in human populations have been developed. The Multifactor Dimensionality Reduction program is a freely available software package that brings together combinations of SNPs and environmental factors into a model that permits detection of nonlinear interactions in the absence of independent main effects.

Although genome-wide association studies currently are a popular method for identifying genes involved in disease risk, the vastness of the data collected and the complexity of the results, combined with difficulties in interpreting these results, may create problems. For example, if three, four, five, or ten SNPs together with three or four environmental factors are important causative factors for cancer, these will not be found in a genome-wide association study, particularly if those factors do not have independent main effects. Genome-wide association studies generate large amounts of information, but ultimately little knowledge. In contrast, a gene-centric approach in which a candidate gene is chosen based on its biological function can generate a great deal of knowledge. A staged knowledge-driven approach will make genome-wide association studies more effective; to do such studies, investigators should first thoroughly explore single gene association studies and pathway-based association studies.

Success with this approach also will require investigators from many different fields to work together. NIH-sponsored workshops have been instrumental in bringing investigators together and prompting them to collaborate on cancer research projects.

In discussion, the following points were raised:

- Detection of complex interactions requires use of analytical tools designed to detect nonlinear patterns. Analysis of hundreds of epidemiological and genetic datasets has shown that in approximately 70 to 80 percent of these datasets, there is significant evidence of nonlinear patterns in the absence of main effects.
- Publication of results from genome-wide association studies has been biased. The results of a number of large, resource-intensive studies on genes associated with diabetes or prostate cancer have been published, but the studies identified only a few genetic risk factors with very small effects.

top

XI. CANCER FROM A GLOBAL PERSPECTIVE—DR. JOE HARFORD

Dr. Joe Harford, Director, Office of International Affairs (OIA), OD, informed members that the National Cancer Act of 1971 provides specific language that mandates that the NCI work internationally, supporting and collaborating in cancer research involving American and foreign participants, as well as training American scientists abroad and foreign scientists in the United States. The NCI's approach to international activities encompasses support for both research and the building of research capacity.

Dr. Harford stated that the NCI's OIA: 1) monitors international activities across the NCI, such as grants and contracts involving foreign investigators and foreign researchers in NCI intramural labs; and 2) manages certain activities involving NCI's international endeavors, including multilateral and bilateral interactions, individual and group training activities, and sponsorship of workshops. Currently, the number of international trainees who are supported in grantee laboratories is not tracked. The largest foreign recipient of NCI grants is Canada. Most grants (58 of 78) that are awarded to foreign PIs go to the United Kingdom and former British Colonies. Only four of the 78 grants were awarded outside of the high-income countries; one each went to India and Senegal, and two went to South Africa. There have been 376 domestic grants and 6 domestic contracts with foreign

components. More than 1,000 people from 74 countries have visited NCI laboratories; 55 percent of them came from the “Asia-4” (Japan, China, Korea, and India). In the lower income countries, however, the training drops off rapidly.

Several described interactions and collaborative efforts between the NCI and many national and international organizations. These include: the International Agency for Research in Cancer (IARC); African Organization for Research and Training in Cancer (AORTIC); International Union Against Cancer (UICC); International Atomic Energy Agency (IAEA); International Network for Cancer Treatment and Research (INCTR); and the World Health Organization (WHO).

He described several examples of multilateral interaction with health diplomacy implications: 1) the Middle East Cancer Consortium (MECC), which just celebrated its 10th anniversary and currently is affiliated with seven cancer registries throughout the Middle East were described. A monograph compared the cancer incidence in several MECC countries with SEER data; this is an important testament to the increasing confidence in the credibility of the data and registries, as well as the collaborative nature of the NCI’s work; 2) a new agreement recently signed between the King Hussein Cancer Center (KHCC) in Jordan and NCI’s CCR, involving building programs, training, informatics, teleconferences, and clinical and basic research capacity; and 3) the Ireland-Northern Ireland NCI Cancer Consortium, which was formed in 1999. In 2006, the Consortium agreement was renewed for an additional 5 years. The Consortium intends to identify infrastructure improvements, formalize and facilitate interactions among the research communities, develop joint programs to enhance the environment for clinical cancer care research and improve patient care, and develop educational exchange programs. Activities include the launch of the All Ireland Cooperative Group, as well as a cooperative network group that is enrolling patients in both their own and industry-sponsored trials in Ireland and within NCI’s U.S. cooperative group system.

Other collaborations include the American Russian Cancer Alliance (ARCA) through its work with the Fox Chase Cancer Center and the University of Maryland Greenbaum Cancer Center and the Breast Health Global Initiative (BHGI), a public-private partnership with Fred Hutchison Cancer Center and the Susan G.

Komen Foundation. The NCI has supported ARCA's infrastructure and tobacco research, cancer communications efforts, and attendance of Russian scientists at the NCI/DCP's Summer Curriculum in Cancer. The BHGI strives to develop and foster the implementation of evidence-based, economically feasible, culturally appropriate guidelines for breast health and has panels on early detection and access, diagnosis and pathology, treatment, and health care systems in public policy. The BHGI produces a range of products, including journal publications and a tiered level (basic, limited, enhanced, and maximal) of treatment resources; for each level of resources, the evidence is examined and an expert panel compiles suggestions for possible interventions.

In discussion, the following points were raised:

- The NCI should define a strategy to address the global cancer problem and determine its level of involvement and role. It should also develop a well-constructed, public health cancer control program. Staff responded that the NCI has begun addressing these issues, including wrestling with budgetary constraints, and that a report to the EC on the topic is imminent.
- The NCI's recent sponsorship of a meeting in Croatia was hailed as a model for work in emerging
- countries, providing a great opportunity for bringing intramural and extramural communities, the advocacy community, and professional societies together.
- The NCI was encouraged to continue pursuing partnership and leveraging opportunities with The Bill & Melinda Gates Foundation. Other organizations also could be approached for funding.
- The Institute of Medicine (IOM) report on cancer in the developing and underdeveloped countries, along with its recommendations, should be disseminated broadly.
- OIA should consider an extramural evaluation of NCI's role in the global cancer problem and pursue public private partnership to support international collaborations.
- Attend the NCI Clinical Trials Cooperative Group Chair meeting to discuss different models and ideas regarding international clinical trials.
- Track the training of internationals in the United States, with a possible aim to foster a network of international researchers by country of origin. The development of a

database of those who trained in the United States would encourage networking and synergy among the trainees.

- Disseminate to BSA members the Executive Committee's forthcoming report on NCI 's role in the world and solicit extramural input on how NCI might obtain a more comprehensive and integrated global approach.

top

XII. FINAL REPORT: NCI BEST PRACTICES FOR BIOSPECIMEN RESOURCES — DRS. ANNA BARKER AND CAROLYN COMPTON

Dr. Compton told members that the NCI Best Practices for Biospecimen Resources Report is a first step for the NCI in a long process built on the realization that biospecimen resources are critical to accelerate the development of molecular-based diagnostics and therapeutics for personalized medicine and translational research in cancer. Key requirements include: 1) best practice-based, data-driven technical and operational standards to ensure quality and enable reproducible molecular analysis; 2) high-quality specimen annotation, including both pathology and clinical data; 3) specimen access for investigators through a timely, centralized, peer-review process; 4) ethical and privacy compliance through a chain of trust; 5) state-of-the-art informatics systems to track specimens, associated data, and patient consents; and 6) communication and outreach efforts to ensure the greatest impact.

The NCI has addressed issues rising from heterogeneity in practices among NCI-supported biospecimen resources that led to a lack of common procedures, standards, management principles, definitions, and computerized access systems, as well as to disparate approaches to ethical, legal, and policy issues. A biospecimen resource is defined as a collection of human specimens and associated data for research purposes, the physical entity in which the collection is stored, and all relevant policies and procedures.

NCI's biospecimen activities began in FY 2002 and the First-Generation Guidelines for NCI-Supported Biorepositories, were reviewed by numerous NIH and DHHS Offices and published in

the Federal Register for public comment. The revised current guidelines, published in April 2007 provides a baseline for operating standards on which to build as the state of the science evolves, unifies policies and procedures for biospecimen resources supported by the NCI or used by NCI-supported investigators, and improves the quality of human biospecimens used in cancer research.

The report provides guidelines for two important areas: 1) the physical aspects of handling specimens and handling data, including the collection and management of clinical data, quality assurance/quality control, biosafety issues, and biospecimen resource informatics; and 2) indicators for the quality of the ethical, legal, and policy aspects that govern the use of specimens, particularly issues related to informed patient consent, access to biospecimens and data, privacy protection and custodianship, and IP.

Dr. Compton noted that the Best Practices Guidelines will be made publicly available on the NCI OBBR Web site and distributed to managers of all NCI-supported intramural and extramural biospecimen resources. A national education and outreach program is planned with regional meetings and user friendly, guidance documents on implementation of best practices will be developed. Research will be conducted to establish the scientific basis for data-driven standards for specimen collection, processing, and storage. This includes a searchable Web-based tool to access biospecimen research data and a partnership with the College of American Pathologists.

In discussion, the following points were raised:

- The final report represents an example of the interaction between the BSA and NCI in producing a quality product at the end of considerable debate and time.
- The NCI was encouraged to develop an appropriately phased approach with education and with the opportunity to achieve compliance before use of the best practices for biorepositories is integrated into grant awards or peer review.
- These practices and guidelines are important steps in collecting data that will help determine appropriate reimbursement and cost recovery issues in the future.

- The NCI should begin communicating the complexity and high expense of adopting the best practices for biospecimens and biorepositories to the broader community.
- Revitalize the BSA Biospecimen Subcommittee to assist with NCI's efforts in utilizing tissue resources, including reimbursement and cost issues, guidelines to produce data and develop patient standards, and a timeline with specific milestones, as well as considerations on how the best practices might be integrated into the peer review process.

top

XIII. ONGOING AND NEW BUSINESS — DR. ROBERT C. YOUNG

No ongoing or new business was discussed.

top

XIV. ADJOURNMENT—DR. ROBERT C. YOUNG

There being no further business, the 37th regular meeting of the Board of Scientific Advisors was adjourned at 11:20 a.m. on Friday, 29 June 2007.

top