

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

45th Meeting

BOARD OF SCIENTIFIC ADVISORS

Minutes of Meeting

**March 8, 2010
Building 31C, Conference Room 10
Bethesda, Maryland**

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

BOARD OF SCIENTIFIC ADVISORS

MINUTES OF MEETING

March 8, 2010

The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 45th meeting on Monday, 8 March 2010, at 8:00 a.m. in Conference Room 10, Building 31C, National Institutes of Health (NIH), and Bethesda, MD. Dr. Richard L. Schilsky, Professor of Medicine, Section of Hematology and Oncology, Biological Sciences Division, University of Chicago Pritzker School of Medicine, presided as Chair. The meeting was open to the public from 8:00 a.m. until 4:23 p.m. on 8 March for the NCI Director's report; a report on NCI Congressional relations; reports on the NCI Patient Navigation Research Program (PNRP) and Nanotechnology Program; and consideration of new and reissuance requests for applications (RFAs), cooperative agreements (Coop. Agr.), and requests for proposals (RFPs) concepts presented by NCI program staff.

BSA Board Members Present:

Dr. Richard L. Schilsky (Chair)
Dr. Paul M. Allen
Dr. Christine Ambrosone
Dr. Michael A. Caligiuri
Dr. Curt I. Civin
Dr. Susan J. Curry
Dr. Chi V. Dang
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
Mr. Don Listwin
Dr. Christopher J. Logothetis
Dr. Kathleen H. Mooney
Dr. James L. Omel

Dr. Edith A. Perez
Dr. Bruce W. Stillman
Dr. Louise C. Strong
Dr. Frank M. Torti
Dr. Jean Y. J. Wang
Dr. James K. Willson

Board Members Absent:

Dr. Andrea Califano
Dr. William S. Dalton
Dr. Robert B. Diasio
Dr. Sanjiv S. Gambhir
Dr. Joe W. Gray
Dr. Timothy J. Kinsella
Dr. Joshua LaBaer
Dr. Robert D. Schreiber
Dr. Stuart L. Schreiber
Dr. Victor J. Strecher
Dr. Irving L. Weissman

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. Richard L. Schilsky	1
II.	Consideration of the 2–3 November 2009 Meeting Minutes—Dr. Richard L. Schilsky	1
III.	Report of the Director, NCI—Dr. John Niederhuber	2
IV.	NCI/Congressional Relations—Ms. Susan Erickson.....	3
V.	Status Report: Patient Navigation Research Program (PNRP)—Drs. Kenneth Chu, Electra Paskett, Mollie Howerton, Richard Roetzheim, and Karen Freund	3
	Introduction—Dr. Kenneth Chu	3
	History and Overview—Dr. Electra Paskett.....	4
	PNRP Interim Analysis Findings—Dr. Mollie Howerton.....	4
	The Moffitt Patient Navigation Research Program—Dr. Richard Roetzheim	5
	Boston University Patient Navigation Research Program—Dr. Karen Freund.....	5
VI.	Status Report: Nanotechnology Program— Drs. Piotr Grodzinski, Angela Belcher, Milan Mrksich, Paul Mischel, and Mark Davis.....	6
	Introduction—Dr. Piotr Grodzinski.....	6
	The Scale of Things: The Solution of Nanotechnology—From a Single Cell to the Body—Dr. Angela Belcher	6
	Nanoscale Constructs for Cancer Therapy—Dr. Milan Mrksich	7
	Towards a Future of Personalized Cancer Care for Glioblastoma Patients Through Development of Novel Molecular Diagnostic Tools—Dr. Paul Mischel.....	7
	Nanoparticles Cancer Therapeutics: From Concept to Clinic—Dr. Mark Davis ...	7
VII.	RFA/Cooperative Agreement Concepts—Presented by NCI Program Staff	8
	Division of Cancer Prevention and Division of Cancer Biology Barrett’s Esophagus Translational Research Network (BETRNet) (RFA/Coop. Agr.)	8
	Office of the Director Commercial Application and Use of Emerging Molecular Analysis Technologies (RFA/Coop. Agr.)	9
	Clinical Proteomic Technologies for Cancer (RFA/Coop. Agr./RFP)	10
VIII.	Adjournment—Dr. Richard L. Schilsky	11

I. CALL TO ORDER AND OPENING REMARKS CDR. RICHARD L. SCHILSKY

Dr. Richard L. Schilsky called to order the 45th 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 2–3 NOVEMBER 2009 MEETING MINUTES DR. RICHARD L. SCHILSKY

Motion: The minutes of the 2–3 November 2009 meeting were approved unanimously.

III. REPORT OF THE DIRECTOR, NCI CDR. JOHN NIEDERHUBER

Dr. John Niederhuber, Director, NCI, welcomed members and provided information about the NCI fiscal year (FY) 2010 and 2011 budgets, establishment of National Cancer Advisory Board (NCAB) working groups, and the EC scientific retreat.

FY 2010 and 2011 Budgets. Dr. Niederhuber reminded members that the NCI FY 2010 operating budget is \$5.103 B, reflecting an increase of \$136 M (2.7%) over the FY 2009 level. The increase will be used for infrastructure costs, science opportunities identified in RFAs, Acquired Immune Deficiency Syndrome (AIDS) target increase, and a new Latin American breast cancer project with co-funding from the Avon Foundation. Budget allocations for FY 2010 include: 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 RPG levels have remained consistent between 2008 and 2009, with unsolicited applications far outnumbering solicited RPGs. Dr. Neiderhuber noted that this was a budget increase in FY2009 and FY2010 after several years of flat budgets. The NIH President's Budget (PB) proposal for FY 2011 includes \$6.036 B to support a range of bold and innovative cancer efforts, including initiation of 30 new drug trials, the doubling of the number of novel compounds in clinical trials, and development of a catalog of cancer mutations for the 20 most common malignancies. The allocation to the NCI totals \$5.26 B or a 3.1% increase. Dr. Niederhuber referred members to the NCI bypass proposal for the FY 2011 budget, which describes the NCI's progress against cancer and provides a resource for the cancer community.

NCAB Working Groups. Dr. Niederhuber informed members that the NCAB recently established two working groups: The Cancer Genome Atlas (TCGA) Working Group, chaired by Dr. Jennifer Pietenpol, Director, Vanderbilt-Ingram Cancer Center; and the *Ad hoc* Working Group To Create a Strategic Vision for the National Cancer Program and Review of the National Cancer Institute (hereafter the Strategic Vision Working Group), co-chaired by NCAB members Mr. William Goodwin, Mr. Robert Ingram, and Dr. Bruce Chabner, and Dr. Phillip Sharp, former NCAB Chair. The Strategic Vision Working Group includes broad representation from academia, industry, and advocacy communities and plans to hold three face-to-face meetings. Sub-working groups will review basic, translational, clinical, and population-based scientific programs. The charge to the working group is to "review the NCI current operating structure and strategic vision to assess the effectiveness of the scientific programs and business management structure of the NCI, in order to determine the gaps and opportunities for delivering scientific progress in understanding, diagnosing, treating, and preventing cancer." The Strategic Vision Working Group will provide a report to the NCAB Activities and Agenda Subcommittee in September 2010.

Executive Committee (EC) Scientific Retreat. The NCI's EC scientific retreat was held in January 2010 to inform NCI's leadership about the directions that cancer research efforts should take to maximize the impact of personalized medicine in clinical care and public health within the context of current cancer research opportunities, patient care priorities, and the health care environment. To create a research community able to undertake complex biological and societal problems, the biology field must adopt a new approach by re-integrating subdisciplines of biology and integrating into biology the sciences of physics, chemistry, engineering, mathematics, and computation. Keynote speaker Dr. Charles Sawyers, Director, Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, defined the science of personalized cancer medicine as the prediction of an individual's risk of cancer along with the best treatment for the individual for a specific cancer. Dr. Sawyers encouraged the NCI to focus on identifying all cancer drug targets within 10 years, advancing the molecular diagnostics field, and building a community network of

molecular pathology centers. Themes covered during the retreat included: 1) biospecimens, patient data, and patient-reported outcomes - needed to inform health care reform; 2) recognition of the contributions of participants in team science; 3) single-agent interventions; 4) and the Cancer Centers and the Specialized Programs of Research Excellence (SPOREs) - should be involved in testing new modalities. The new biology will be accomplished by team science, with a convergence of individual laboratories and academic institutions. Translation will be facilitated by the public-private partnership and a reengineered clinical trials system that allows testing of combination therapies.

In the discussion, the following points were made:

- < New molecular diagnostic activities are being funded with American Recovery and Reinvestment Act (ARRA) funds to develop standards and provide leadership in the characterization of the patient and the patient's disease, particularly through Cancer Human Biobank (caHUB) and expedited by technology.
- < The NCI is monitoring the submission of applications to determine the effect of ARRA funds and at present has not seen a significant rise in grant application submissions.

IV. NCI/CONGRESSIONAL RELATIONS **ScMS. SUSAN ERICKSON**

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), informed members that the FY 2010 appropriations totaled \$31 B for the NIH and \$5.1 B for the NCI. The PB for FY 2011 was announced on 1 February, with \$32.09 B for the NIH and \$5.26 B for the NCI. Ms. Erickson provided an update on NCI testimonies, upcoming hearings, and legislation of interest, including the Small Business Innovation Research (SBIR) Reauthorization bill and the Access to Cancer Clinical Trials Act.

In the discussion, the following point was made:

- < The NCI has reengineered its SBIR program by leveraging private sector investment through the Phase IIb program. Because of its success, the NCI SBIR program is being considered as a possible model for SBIR programs throughout the government.

**V. STATUS REPORT: PATIENT NAVIGATION RESEARCH PROGRAM (PNRP)—
DRS. KENNETH CHU, ELECTRA PASKETT, MOLLIE HOWERTON, RICHARD
ROETZHEIM, AND KAREN FREUND**

Introduction—Dr. Kenneth Chu

Dr. Kenneth Chu, Chief, Disparities Research Branch, Center to Reduce Cancer Health Disparities (CRCHD), introduced the PNRP. The PNRP seeks to help vulnerable populations work within the U.S. health care system by helping translate medicine into lay language, informing patients about health care system pathways, increased access to clinical trials, and assisting with physical needs and other barriers to care. Dr. Chu next introduced the speakers: Drs. Electra Paskett, Principal Investigator (PI), Ohio State University Comprehensive Cancer Center; Mollie Howerton, CRCHD; Karen Freund, PI, Boston University School of Medicine; and Richard Roetzheim, PI, Moffitt Cancer Center and University of South Florida.

History and Overview—Dr. Electra Paskett

Dr. Paskett informed members that the PNRP connects navigators with cancer patients to navigate the health care system and access appropriate social and financial services, ensuring that individuals receive timely diagnosis and treatment. She informed members that the PNRP includes nine institutions across the United States and focuses on breast, cervical, colorectal, and prostate cancers. The Program is examining whether navigated patients receive more timely and definitive resolution following screening as well as more timely treatment following a positive diagnosis; and whether their satisfaction regarding their health care system experience is improved. PNRP's target populations (African American, Hispanic, other minority, and low-income populations) were contacted either via telephone or through a combination of in-person and telephone. Recruitment strategies centered on building trust and relationships, and local training was expanded through national workshops and Web-based trainings. The PNRP has developed a data dictionary and other tools and resources for patients and providers, and it serves as a model of partnership and collaboration across the NCI, NIH, American Cancer Society (ACS), and other foundations. Site-specific partnerships and collaborations have been established with community-based organizations, universities, and governmental agencies to help ensure program sustainability.

PNRP Interim Analysis Findings—Dr. Mollie Howerton

Dr. Howerton described research progress made in the navigation of patients with breast and cervical cancers during the past 2 years. The breast cancer study enrolled more than 3,700 women with abnormal breast findings, of whom 1,700 participated in the navigated arm. The majority of enrolled patients ranged between 40 and 63 years, were Hispanic, and were either uninsured or enrolled in public insurance. Median time to diagnostic resolution by racial and ethnic group showed a statistically significant downward slope for Hispanic and African American women who received navigation, but minimal or no effect on other minorities or Whites. Median time to diagnostic resolution by insurance showed reduced time for those uninsured or with public insurance for the navigated arm, but an increase for women with private insurance. To date, approximately 9 percent of the navigated patients and 4 percent of the non-navigated patients had abnormal findings that were diagnosed as cancer; demographically, these women were similar to the total sample of women in the study.

The cervical cancer study included 1,475 women, with the majority of patients enrolled under 35 years old, approximately one-half were Hispanic, and 75 percent were either uninsured or on public insurance. Of the 909 women enrolled in the navigated arm, 7 percent were diagnosed with cervical cancer, with most being under age 35 and included a higher proportion of Hispanic women. Median time to diagnostic resolution showed a downward slope for African American and Hispanic women who received navigation. Of the 566 women in the non-navigated arm, 13 percent were diagnosed with cervical cancer.

Significant barriers to diagnostic resolution that were reported include: language, adult care, disability, employment, perception of tests and treatment, communication, fear, location of health care facilities, and transportation. Interim findings show that navigation may decrease the time to diagnostic resolution for African Americans, Hispanics, and uninsured patients. In-person navigation may be a useful strategy for reducing time when three or more barriers are present; for two or fewer barriers, telephone navigation may be sufficient to reduce time to diagnostic resolution.

The Moffitt Patient Navigation Research Program—Dr. Richard Roetzheim

Dr. Roetzheim described the Moffitt PNRP study, which focused on navigating breast and colorectal cancer patients in 12 health care clinics that provide services to disadvantaged and migrant farm populations in west central Florida. More than 1,300 patients enrolled in the study, of whom 616 received navigation while 738 enrolled in the control arm, and 53 participants were diagnosed with cancer. Patient characteristics included 93 percent female, 54 percent Hispanic ethnicity, and 11 percent African American, with low levels of education and income and the majority on public insurance or uninsured.

A lay-person, intensive navigation model was employed, in which navigators were selected based on knowledge of the community and health care system; patients were navigated through in-person encounters and via telephone with 10 encounters on average. Participants cited an average of six barriers to care with the most common obstacles being insurance, fear, language, and health literacy, communication, and location of health care facility. Diagnostic resolution for abnormal breast screenings totaled 88 percent for navigated patients and 78 percent for the control arm. The effects of navigation on psychosocial distress associated with an abnormal cancer screening test were studied and showed a reduction in perceived stress and depression and a perception by patients of greater control in the navigated arm.

Boston University Patient Navigation Research Program—Dr. Karen Freund

Dr. Freund described Boston University's PNRP study which is organized within the sites of primary care and uses a care management model to identify cases, assess barriers to care, develop individual care plans, and track through diagnostic resolution. An electronic patient navigator template was developed to facilitate the process, and encounters were initiated via telephone to allow more focused resources for specific patients. Analyses being conducted on social networks have shown that navigators facilitate care with patients, providers, nonclinical staff, and other outside support agencies. The effect of race-ethnicity on barrier identification was nearly 80 percent of non-White (i.e., Hispanic, Black, and Asian) patients reported one or more barriers compared to 50 percent of White patients. Interim analysis of time to resolution for breast patients has shown a significant benefit of navigation over the control conditions and those with more severe abnormalities receiving care more quickly. Dr. Freund informed members that navigation seems to have the greatest benefit for patients whose diagnostic time resolution exceeds 60 days.

Dr. Chu concluded by informing members that the PNRP has been successful in recruiting diverse and underserved populations and beneficial in assessing models for navigation delivery and for developing tools that can be used by others for patient navigation. He informed members that the next steps include analysis of the final data and examining best practices and tools across the spectrum of navigation delivery to broaden the outcome measures and understand the role of patient navigation in the health care system.

In the discussion, the following points were made:

- < The NCI should consider focusing research on determining “markers” to identify patients likely to benefit from patient navigation. Identification of characteristics of patients with long diagnostic resolution times may be helpful.

- < The PNRP should evaluate the extent to which health disparities might be impacted by differences in access to molecular diagnostic tests. Small pilot projects on access and acceptability of molecular diagnostic tools should be considered.
- < Patient navigation should be prioritized by diseases that are time sensitive to diagnosis, with an emphasis on achieving early diagnosis.
- < Staff was encouraged to compile and present cost and other data by site, rather than aggregated across sites, to ensure differences can be evaluated.

VI. STATUS REPORT: NANOTECHNOLOGY PROGRAM—DRS. PIOTR GRODZINSKI, ANGELA BELCHER, MILAN MRKSICH, PAUL MISCHER, AND MARK DAVIS

Introduction—Dr. Piotr Grodzinski

Dr. Piotr Grodzinski, Director, Nanotechnology for Cancer Program, provided an overview of the NCI Alliance for Nanotechnology in Cancer. Dr. Grodzinski informed members that the Alliance supports translational research to develop ways to use nano-materials to develop new ways to detect cancer, understand the progression of the disease, and improve delivery and efficacy of cancer therapeutics. The Alliance has 8 Centers of Cancer Nanotechnology Excellence and 12 Cancer Nanotechnology Platform Partnerships. Phase II has expanded the initiative to include multidisciplinary training awards. In addition, the Nanotechnology Characterization Laboratory in Frederick, MD, works with the Food and Drug Administration (FDA) and National Institute Standards and Technology (NIST) to develop and standardize characterization methodology for nano-materials. The Alliance has produced more than 1,000 peer-reviewed journal articles; established 8 clinical trials; developed commercialization partnerships with 50 plus companies; and filed more than 200 disclosures and patents. The Alliance also has obtained additional funding from grants, industry, and venture capital investors. Dr. Grodzinski introduced the speakers: Drs. Angela Belcher, Massachusetts Institute of Technology (MIT); Milan Mrksich, University of Chicago; Paul Mischel, University of California, Los Angeles (UCLA); and Mark Davis, California Institute of Technology.

**The Scale of Things: The Solution of Nanotechnology—From a Single Cell to the Body—
Dr. Angela Belcher**

Dr. Belcher described how her laboratory uses nanotechnology to reprogram the M13 deoxyribonucleic acid (DNA) virus to serve as a multifunctional genetic template to target cancer antigens and deliver substances such as magnetic resonance imaging (MRI) contrast agents, which improves visualization of tumors. She stated that the M13 phage has been engineered to target the tumor antigen secreted protein acidic rich in cysteine (SPARC) and take up functionalized iron oxide nanoparticles, which improved specificity and image resolution. M13 phage also have been engineered to incorporate single walled carbon-nanotubes (SWNT), which will be useful for *in vivo* imaging since the signal to noise tissue background is improved by 100 fold. M13 phage with binding affinity for SWNTs can be used to target and deliver chemotherapy molecules to the tumor site. The use of phage to target tumors more specifically may allow use of lower doses of chemotherapeutic drugs while still maintaining efficacy.

Nanoscale Constructs for Cancer Therapy—Dr. Milan Mrksich

Dr. Mrksich described work in his laboratory to improve diagnosis of prostate cancer through the development of a “bio-barcode assay” that uses gold nanoparticles to detect prostate specific antigen (PSA) with a 300-fold increase in the level of detection. A trial is underway to test the ability of this assay to monitor PSA in post-operative prostate cancer patients. Gold nanoparticles also were used as antisense reagents to deliver DNA or siRNA to modulate gene expression; unlike traditional delivery techniques, use of nanoparticles eliminates the need for co-administration of delivery agents. Small interfering RNA (siRNA) gold nanoparticles were designed to target messenger RNAs (mRNAs) expressed in breast cancer cells and, as a result of gene silencing, increase apoptosis and decrease proliferation. Nano-materials also have been incorporated into assays to detect targets of deacetylase activity, a process essential for epigenetic gene regulation, which is increasingly realized to be important in cancer. These assays were used to screen peptide libraries to identify specificity profiles for deacetylases. The NCI Alliance for Nanotechnology has been instrumental in supporting this work and has allowed collaboration with a number of different companies and thus translation and commercialization of these research findings.

Towards a Future of Personalized Cancer Care for Glioblastoma Patients Through Development and Implementation of Novel Molecular Diagnostic Tools—Dr. Paul Mischel

Dr. Mischel described the use of DNA-encoded antibody libraries (DEAL) to subdivide a tumor into well-defined cell populations for molecular marker analysis. Once the tumor cell subpopulations are separated, DNA, RNA, and proteins in those populations can be analyzed to characterize the tumor. Use of DEAL technology revealed coactivation of glioblastoma multiforme (GBM) “core pathways” in a tumor subpopulation defined by epidermal growth factor receptor (EGFR) expression. DNA copy number alterations and mutations in three core pathway genes were found in more than 80 clinical specimens. DEAL can detect rare tumor cells in histologically normal tumor margins that cannot be detected by pathological examination and molecular analysis of bulk tumor tissue. The technology can be used to perform quantitative proteomic measurements and quantitative analysis of signal transduction at the single-cell level.

Dr. Mischel noted that an integrated blood barcode chip (IBBC) to use for noninvasive, real-time monitoring of response to targeted therapy for GBM had been designed. This technology was used in a clinical trial to stratify GBM patients as responders or nonresponders to avastin therapy. Proteomic analysis of 21 proteins identified three clusters of patients; tumor growth during avastin therapy was observed in 100 percent of patients in cluster 1, while tumor growth occurred in less than 20 percent of patients in clusters 2 and 3.

Nanoparticle Cancer Therapeutics: From Concept to Clinic—Dr. Mark Davis

Dr. Davis described the use of nanoparticles for targeted delivery of chemotherapy drugs by protecting drugs from degradation and bypassing multidrug resistance mechanisms that involve cell surface pumps. Cyclodextrin (CD) polymer nanoparticles were used to deliver camptothecin (CPT) to the tumor which previously failed in the clinic due to toxicity. The particles persist primarily in the area to which they were targeted (tumor tissue), thus protecting healthy tissue. Phase 1 safety and pharmacokinetic analyses of CD-camptothecin nanoparticles for treatment of advanced solid tumors found extended duration of drug levels in plasma and no severe side effects even when frequent dosing schedules were used.

Nanoparticles can be used to deliver targeted siRNAs to tumor cells, where the siRNAs block expression of mRNAs needed for tumor growth and survival. Nanoparticles containing siRNA that targeted ribonucleotide reductase subunit M2 (*RRM2*) was created using transferrin as the targeting molecule, which is expressed more highly in tumors. In a clinical trial involving patients with solid tumors refractory to standard care, dose-dependent localization of nanoparticles was observed, as well as efficient knockdown of target *RRM2* mRNA and protein. This is the first formulated, targeted, systemic siRNA to enter clinical trials. In summary, nanoparticle therapeutics enable the use of drugs that previously failed toxicity studies and provides for new combination therapies.

In the discussion, the following points were made:

- < The National Science Foundation (NSF) funds nanotechnology centers that focus on materials work and some materials fabrication and processing. The NCI's interaction with NSF efforts occurs through investigators who have grants funded by both organizations.
- < Input from oncologists to optimize nanotechnology for cancer detection and treatment, and consider the development of an education program to inform clinicians about the potential applications of nanotechnology should be obtained. Staff indicated that the Alliance has plans for more input by clinicians.
- < Consideration should be given to establishing ways to measure the value of NCI's investment in individual nanotechnology investigators who work in team science versus individual R01s. Outcomes should a primary metric for success.

VII. RFA/COOPERATIVE AGREEMENT CONCEPTS PRESENTED BY NCI PROGRAM STAFF

**Division of Cancer Prevention (DCP) and Division of Cancer Biology (DCB)
Barrett's Esophagus Translational Research Network (BETRNet) (RFA/Coop. Agr.)**

Dr. Peter Greenwald, Director, DCP, presented recommendations made by the Barrett's Esophagus Translational Research (BETR) Working Group to create an RFA to fund a multidisciplinary, multi-institution translational research network to accelerate research on Barrett esophagus (BE) and esophageal adenocarcinoma (EA) and clinical translation of research findings. Dr. Greenwald informed members that incidence of EA in the United States is increasing faster than that of any other cancer. Gastric reflux, obesity, and tobacco use contribute to EA risk, while use of non-steroidal anti-inflammatory drugs and *Helicobacter pylori* infection appear to confer protection. BE lesions develop into EA; and the relative ease in accessing BE and AE lesions and their response to interventions make this cancer an ideal model for studying carcinogenesis and protective factors.

BETRNet would include four translational research areas of focus: 1) biology of EA carcinogenesis; 2) development of novel technologies and methods; 3) patient outcome-associated biomarkers; and 4) development and validation of molecularly targeted interventions. The Cooperative Agreement funding mechanism would promote partnership with the NCI, ensure collaboration, and lead to development of a centralized patient registry.

Subcommittee Review. Dr. James K. Willson, Director, Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, expressed the Subcommittee's support for the

concept. Dr. Willson noted that the disease has a significant morbidity associated with its discovery at a later stage and a poor survival rate. A network of collaborators in the clinical setting and access to clinical tissues with long term follow up will benefit translational research efforts. Subcommittee issues included: the coordination of access to clinical tissues and other biospecimens; possible overlap or collaboration with other NCI initiatives (Barrett's and Esophageal Adenocarcinoma Consortium [BEACON], Early Detection Research Network [EDRN], TCGA, etc.); limited impact on esophageal cancer rates; and a likely increase in the use of ablation treatment earlier in the disease.

The first year cost is estimated at \$7 M for 4 Translational Research Centers (U01) and a Coordinating Center (U24), with a total cost of \$35 M for 5 years.

In the discussion, the following points were made:

- < The BETRNet clinical tissues and other biospecimens will be coordinated through a virtual repository and will be available to investigators outside the network.
- < EDRN, which examines early detection methods, has a different objective than BETRNet and does not have a translational-to-clinical research focus.
- < Exit strategies should be instituted across the entire NCI portfolio of activities, particularly for large programs.
- < BE incidence has increased even in developed countries, with lifestyle factors as well as interactions between antibiotics and *H. pylori* eradicationis believed to have an impact.

Motion. A motion to concur on the DCP and DCB's RFA/Coop. Agr. entitled "Barrett's Esophagus Translational Research Network (BETRNet)" was approved with 15 yeas, 5 nays, and 3 abstentions.

Office of the Director

Commercial Application and Use of Emerging Molecular Analysis Technologies (RFA/Coop. Agr.)

Mr. Michael Weingarten, Director, NCI SBIR Development Center, described a new SBIR/Small Business Technology Transfer (STTR) concept to support the Innovative Molecular Analysis Technologies (IMAT) Program. Mr. Weingarten informed members that the IMAT Program's mission is to stimulate high risk/high impact research by supporting early-stage development of next generation molecular and cellular analysis technologies. The Program's thematic areas include: 1) innovative technology development for cancer research; 2) application of emerging technologies for cancer research; and 3) innovative and applied emerging technologies and biospecimen science. The SBIR/STTR concept focuses on the commercial validation of molecular analysis technologies and supports the pursuit of commercially relevant milestones. A new requirement is the application must include feasibility data or a prototype. A significant emphasis will be placed on the commercialization aspects of the grant. Members were told that the NCI has established a development center that focuses exclusively on the management of its SBIR/STTR portfolio and that program staff assist with outreach, company mentorship, grant follow up, relationship building, regulatory assistance, and commercialization.

Subcommittee Review. Dr. Marc A. Kastner, Dean, School of Science, Donner Professor of Science, MIT, expressed the Subcommittee’s support for the concept. Dr. Kastner pointed out that the NCI’s SBIR/STTR program could be used as a model for SBIR programs in the NIH and other federal agencies, and he applauded the emphasis on mentorship and follow up for grantees, as well as clear expectations and the evaluation process. The Subcommittee also appreciated the incorporation of the SBIR/STTR program within NCI’s overall strategic approach and the IMAT continuum of support from inception through commercialization of technology, particularly bridging the gap between the academic enterprise and full commercialization.

The first year cost is estimated at \$2 M for 5–7 awards, with a total cost of \$4 M for 2 years.

In the discussion, the following points were made:

- < Members encouraged staff to extend the length of the Phase II award from 2 to 3 years.
- < The Bridge Program or Phase IIb, which provides a means to maintain the momentum of innovative technology development en route to commercialization, requires that the PI must obtain matching funds from an external source, such as a strategic partner or angel investor. Grantees applying for Phase IIb awards must first complete Phases I and II.

Motion. A motion to concur on the Office of the Director’s RFA/Coop. Agr. entitled “Commercial Application and Use of Emerging Molecular Analysis Technologies“ was approved unanimously.

Clinical Proteomic Technologies for Cancer (RFA/Coop. Agr./RFP)

Dr. Anna Barker, Deputy Director for Advanced Technology and Strategic Partnership, described the reissuance concept for the Clinical Proteomic Technology Assessment for Cancer (CPTAC) Program. Dr. Barker told members that the CPTAC initiative was launched in 2006 to address technical barriers related to discovery and verification in proteomics, as well as issues concerning biospecimens, statistical issues in experimental design, data acquisition and analysis, and lack of standards and high-quality reagents. The Program operates nationwide through a Center network that emphasizes team science and integrates multiple disciplines. Key accomplishments include standardization and transferability of mass spectrometry, public data portal, community reagents, data release policies, scientific output (e.g., seven patents and more than 170 papers), and leveraged funding. An independent evaluation report noted that CPTAC has achieved significant milestones and has long-term potential as a key component in proteomics for personalized medicine. A strategic workshop recommended that the next phase should build on genomic alterations discovered by TCGA and other similar efforts in the context of protein biology, as well as advance proteomic efforts by enabling technology development.

Dr. Barker stated the reissuance concept is based on Phase I lessons learned and accomplishments. The objectives are to: 1) identify highly credentialed biomarker candidates for qualification studies; 2) develop a library of characterized and verified protein analytes with genomic correlation; and 3) conduct quantitative multiplex assays with datasets, reagents, and standard operating procedures. Milestones to ensure that the next phase of CPTAC provides a resource of characterized and verified protein analytes (genomic correlation), cross-tested within a network, and shared with the

public for further development as potential cancer biomarkers will be defined.

Subcommittee Review. Dr. Jean Wang, Distinguished Professor of Medicine, University of California, San Diego (UCSD) School of Medicine, and Associate Director of Basic Research, Moores UCSD Cancer Center, informed members that CPTAC Phase I is achieving its milestones but noted the limitations of tandem mass spectrometry as a technology that enables quantitative sensitive discovery of clinically actionable biomarkers. Dr. Wang recommended that the goals of the CPTAC network should be clarified in terms of future milestones or scientifically driven clinical goals of the biomarker discovery effort. Concerns were expressed about the application of the technologies to clinical cancer, transferability from work in serum samples to TCGA's tissue specimens, and the concept's emphasis on technology rather than biomarker discovery. Further reservations included the use of mass spectrometry as the sole technology and the absence of specific hypotheses to focus research. The Subcommittee encouraged a concept that reflects a balance of patient and biological outcome-driven science and technology development.

The first year cost is estimated at \$24 M for 6-8 U24 awards and \$2.5M for a reagent contract with a total cost of \$120 M for U24 awards and \$12.5M for contracts for 5 years.

In the discussion, the following points were made:

- < NCI staff confirmed a high likelihood that the technology development that has been achieved thus far can be easily adapted or transferred from studies in serum and plasma to studies in tissue.
- < Proteomic datasets of TCGA specimens would be of greatest use for research addressing clinical or biological hypotheses that include comparative analyses.
- < Members expressed consensus for technology and targeted assay development and encouraged a hypothesis-driven biomarker and clinical endpoint-driven approach. Concerns were voiced about the predominant use of mass spectrometry for tissue analysis.

Motion. A motion to concur on the Office of the Director's RFA/Coop. Agr./RFP entitled "Clinical Proteomic Technologies for Cancer" was approved unanimously with the caveat that the concept would be revised to reflect a greater focus on biomarker development and that the Concept Review Subcommittee concur with the revisions.

VIII. ADJOURNMENT **CDR. RICHARD L. SCHILSKY**

There being no further business, the 45th regular meeting of the Board of Scientific Advisors was adjourned at 4:23 p.m. on Monday, 8 March 2010.