

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

**43<sup>rd</sup> Meeting**

**BOARD OF SCIENTIFIC ADVISORS**

**Minutes of Meeting**

**June 22, 2009  
Building 31C, Conference Room 10  
Bethesda, Maryland**

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

**BOARD OF SCIENTIFIC ADVISORS**

**MINUTES OF MEETING**

**June 22, 2009**

The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 43<sup>rd</sup> meeting on Monday, 22 June 2009, at 8:00 a.m. in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Robert C. Young, Chancellor, Fox Chase Cancer Center, presided as Chair. The meeting was open to the public from 8:00 a.m. until adjournment at 4:00 p.m. on 22 June for the NCI Director's report; a report on NCI Congressional relations; recognition of departing BSA members; an update on clinical proteomic technologies for cancer; a report on NCI's functional platform toward highly personalized cancer medicine; discussion of the NCI Listens program and the NIH stem cell policy; and consideration of request for applications (RFAs) new and reissuance concepts and request for proposals (RFPs) new concepts presented by NCI Program staff.

**BSA Board Members Present:**

Dr. Robert C. Young (Chair)  
Dr. Paul M. Allen  
Dr. Christine Ambrosone  
Dr. Kirby I. Bland  
Dr. Curt I. Civin  
Dr. Susan J. Curry  
Dr. William S. Dalton  
Dr. Robert B. Diasio  
Dr. Kathleen M. Foley  
Dr. Sanjiv S. Gambhir  
Dr. Todd R. Golub  
Dr. Joe W. Gray  
Dr. Leland H. Hartwell  
Dr. James R. Heath  
Dr. Mary J. C. Hendrix  
Dr. Marc A. Kastner  
Dr. Timothy J. Kinsella  
Dr. Christopher J. Logothetis  
Dr. James L. Omel  
Dr. Edith A. Perez

Dr. Richard L. Schilsky  
Dr. Stuart L. Schreiber  
Dr. Ellen Sigal  
Dr. Bruce W. Stillman  
Dr. Victor J. Strecher  
Dr. Louise C. Strong  
Dr. Jean Y. J. Wang  
Dr. Jane Weeks  
Dr. Irving L. Weissman  
Dr. James K. Willson

**Board Members Absent:**

Dr. Andrea Califano  
Dr. Michael A. Caligiuri  
Dr. Leroy Hood  
Dr. Kathleen H. Mooney  
Dr. Robert D. Schreiber

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

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### I. CALL TO ORDER AND OPENING REMARKS-DR. ROBERT C. YOUNG

Dr. Robert C. Young called to order the 43<sup>rd</sup> regular meeting of the BSA and welcomed current and new 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. 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 MARCH 2009 MEETING MINUTES-DR. ROBERT C. YOUNG

**Motion:** The minutes of the 2B3 March 2009 meeting were approved unanimously.

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

Dr. John Niederhuber, Director, NCI, welcomed members and provided a report on the NCI’s most challenging issues: the American Recovery and Reinvestment Act of 2009 (ARRA), the NCI budget, and the trans-NIH cancer strategic plan.

**ARRA 2009.** Members were reminded that the ARRA, which was signed into effect on 17 February 2009, allocated \$10.4B to the NIH, of which \$1.257B went to the NCI, \$1B to extramural construction, \$500M to NIH construction, \$300M to shared instrumentation, \$400M to comparative effectiveness research (CER) (with an additional \$400 M to the Department of Health and Human Services (HHS) and \$300M to

the Agency for Healthcare Research and Quality [AHRQ]), and \$800M to the NIH Office of the Director (OD). The NCI is working to meet ARRA's goal of maintaining and increasing jobs while funding the best new science and investing in science that will impact patients. In fiscal year (FY) 2009, investigators were funded up to the 25<sup>th</sup> percentile, i.e., the Research Project Grants (RPGs) payline is at the 16<sup>th</sup> percentile, increased to the 18<sup>th</sup> percentile through 4-year grants funded from ARRA and followed by appropriated dollars, and further increased to the 25<sup>th</sup> percentile through a mixture of 2-year and 4-year grants that are supported by ARRA funds for the initial 2 years. Approximately 50 ARRA funding announcements have been posted and made available to the community to apply for NCI support. The NIH received approximately: 20,000 ARRA Challenge Grant applications (approximately 4,400 are cancer relevant), and 2,500 Grand Opportunity (GO) grants (more than 550 are cancer related). Dr. Niederhuber indicated that it is presumed that next fiscal year many of the unsuccessful Challenge and GO grant submissions would be submitted as investigator initiated grants. He noted that grants that are ready to be awarded are submitted weekly through the NIH to the White House, and that most grants are officially awarded about 2 weeks following their inclusion on the weekly list. Members also were informed that NCI planned on committing the majority of ARRA funds in FY2009 and that all funds must be spent by the end of FY 2010.

Dr. Niederhuber informed members that the Federal Coordinating Council for CER, which coordinates CER and related health services research across multiple agencies, has prepared a draft definition: "Comparative effectiveness is the conduct and synthesis of systematic research comparing different interventions and strategies to prevent, diagnose, treat and monitor health conditions...." He also informed members that the 15-member Council held a public "listening" session on 14 April and will submit an operating plan to the House and Senate Appropriations Committees by the end of July 2009. Additionally, the Institute of Medicine (IOM) will submit a consensus report on CER by the end of June 2009 that provides recommendations to Congress and the Secretary for the expenditure of CER funds.

**FY 2009 and 2010 Budgets.** Dr. Niederhuber described the NCI's FY 2009 operating budget, which was set by the FY 2009 Omnibus Appropriations Bill at \$4.968B, reflecting an increase of 2.9 percent (\$138M) over FY 2008 levels. He reviewed the policies that the NCI has followed in developing and revising its budget and noted that the Institute will award more competing RPGs than in FY 2008 with an increase from 1,284 to 1,412. In addition, there is a 3 percent increase above current levels for Type-2 grants and a 5 percent increase above current levels for grants recommended for up to 7 modules, as well as a reduction of approximately 17 percent of Type-1 level requested amounts. The FY 2010 President's Budget proposes \$5.15B for the NCI, representing a 3.5 percent (\$181M) increase.

**Trans-NIH Cancer Strategic Plan.** Members were told that NIH had appointed him and Dr. Stephen Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), to chair a committee to develop the Trans-NIH Cancer Strategic Plan. All Institutes and Centers (ICs) that conduct cancer research (24 of 27 ICs) have submitted information on how their Institutes would support cancer research with increased resources, and the report is being prepared for submission to the NIH on 26 June.

Dr. Niederhuber concluded that the ARRA funding will continue to require monitoring and adjustment, particularly to ensure support for projects in years beyond the ARRA funding, and he noted that the proposed doubling of the NIH cancer budget will present further unique challenges.

**In the discussion, the following points were made:**

- < The extramural community should be provided with information about the probability of funding success for special initiatives prior to application.
- < Members encouraged the NCI to establish a mechanism to address accountability and responsibility for monitoring trans-NIH cancer research.

- < Members asked how NCI works with other government agencies, such as the U.S. Department of Defense (DoD) and the Department of Energy (DOE), that support cancer research. It was noted that NCI is currently enhancing relationships with these agencies, including the new Walter Reed Medical Institute.
- < The NCI allocation of ARRA funds mostly mirrors the allocation of its operational budget.
- < Contracts are awarded following a competitive peer review process. Members encouraged the NCI to maintain rigorous oversight of the use of this mechanism.
- < Members expressed concern regarding the percentage of cancer research dollars across NIH and requested assurance that the NCI budget not decrease with the proposed \$11B trans-NIH cancer budget allocation.

#### **IV. NCI/CONGRESSIONAL RELATIONS-MS. SUSAN ERICKSON**

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), informed members that the President's Budget for FY 2010 includes \$30.8B for the NIH, \$5.15B for the NCI, and \$6B for NIH cancer-related research; House and Senate Subcommittees are considering allocations and drafting bills for FY 2010 appropriations. Ms. Erickson described legislation of interest, including the 21<sup>st</sup> Century Cancer Access to Life-Saving Early Detection Research and Treatment (ALERT, also the Kennedy Cancer Bill, S. 717) and several CER bills. She noted that the Tobacco Bill (H.R. 1256) has been approved by the House and Senate and awaits President Obama's signature; and Congressional priorities are the appropriation bills and health care reform.

##### **In the discussion, the following point was made:**

- < The forthcoming IOM report provides guidance to the Department of Health and Human Services (DHHS) Secretary regarding the ARRA specified CER funds that are being overseen by the DHHS, AHRQ, and NIH, as well as long-term CER planning. Future CER efforts are being considered by Congress in various bills proposed by Sen. Edward Kennedy (D-MA), Sen. Max Baucus (D-MT), Rep. Kurt Schrader (D-OR), and Rep. Henry Waxman (D-CA).

#### **V. RECOGNITION OF DEPARTING MEMBERS—DRS. JOHN NIEDERHUBER AND ROBERT C. YOUNG**

On behalf of the NCI, Drs. Niederhuber and Young recognized the contributions of six retiring BSA members: Drs. Kirby I. Bland, Fay Fletcher Kerner Professor and Chairman, Department of Surgery, University of Alabama, Birmingham School of Medicine; Leland H. Hartwell, President and Director, Fred Hutchinson Cancer Research Center, University of Washington; Leroy Hood, President and Founder, Institute for Systems Biology; Ellen V. Sigal, Chairperson, Friends of Cancer Research; Jane Weeks, Professor of Medicine and Chief, Division of Population Sciences, Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School; and Robert C. Young, Chancellor, Fox Chase Cancer Center. Dr. Niederhuber acknowledged the importance of their contributions to the success of the Institute, and recognized the valuable volunteer hours that each provides to the NIH and the NCI.

#### **VI. UPDATE: CLINICAL PROTEOMIC TECHNOLOGIES FOR CANCER—DRS. JOE W. GRAY, DANIEL LIEBLER, STEVEN CARR, DAVID RANSOHOFF, AND HENRY RODRIGUEZ**

##### **Introduction**

Dr. Joe W. Gray, Lawrence Berkeley National Laboratory, described the NCI's efforts to improve discovery of cancer protein biomarkers. Dr. Gray informed members that the Clinical Proteomics

Technologies for Cancer (CPTC) program was established in October 2006 to support biomarker development and address the issues identified as significant barriers to progress that include: 1) experimental design; 2) technological or technical barriers; 3) biospecimen collection; and 4) data acquisition, analysis, and reporting. The Clinical Proteomics Technology Assessment Center Network involves 5 major centers and a number of allied institutions. Dr. Gray introduced the other speakers: Drs. Daniel Liebler, Vanderbilt University School of Medicine; Steven Carr, Broad Institute of Massachusetts Institute of Technology (MIT) and Harvard University; David Ransohoff, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill; and Henry Rodriguez, Director, CPTC.

### **Performance and Optimization of Liquid Chromatography (LC)-Mass Spectrometry (MS)/MS Platforms for Unbiased Discovery of Biomarker Candidates**

Dr. Liebler stated that the intra-laboratory analyses of LC-MS/MS technology is to improve protein biomarker discovery. He noted that this technology will be used to survey, identify, quantify, and compare protein complements in normal and cancer tissues. Shotgun proteomics, the primary technology used, involves digesting proteins to generate complex mixtures of peptides, fractionation of the mixture using chromatography, and using the mass spectrometer to acquire fragmentation or MS/MS spectra of the peptides and compare them against databases of known peptide and protein sequence spectra. The major challenge is querying a highly complex mixture of peptides present in a broad range of concentrations. In addition, the use of multiple instruments required for this approach contributes to significant variability in detection. A Human Proteome Organization (HUPO) study found that only 7 of 27 laboratories could correctly identify all 20 proteins present in a complex protein mixture. With coaching, all 27 laboratories correctly identified “most” of the proteins. This raised questions as to whether the technology was inherently variable, sources of variability, and reproducibility of analyses of complex proteomes.

The CPTC Unbiased Discovery Work Group plans to evaluate and standardize the performance and use of proteomic discovery platforms. The initial focus was on standardizing instruments and developing standard operating procedures (SOPs) by having each test site characterize a *Saccharomyces cerevisiae* protein extract spiked with 48 proteins. Run-to-run repeatability (e.g., the consistency of results from multiple experiments performed on the same instrument) in analyses of the protein extract across 7 instruments/sites was between 65 and 80 percent. Reproducibility across laboratories was between 65 and 70 percent. In conjunction with the National Institute of Standards and Technology (NIST), over 42 LC-MS performance metrics were monitored to diagnose and correct system malfunctions. These data were used to develop 42 performance metrics and a software toolkit to monitor and troubleshoot system performance, which will be made available to the community. Standardizing instrument performance and analytic approaches helped improve consistency of results.

### **Protein Quantitation by Targeted MS: The Bridge From Discovery to the Clinic**

Dr. Carr described a new technology, Multiple Reaction Monitoring-MS (MRM-MS), which uses protein fractionation and MS to define a genome- or proteome-unique set of peptides. The peptides are compared to isotopically labeled standards to quantify peptides of interest across samples. Tens to hundreds of peptides can be simultaneously quantified. Coupling MRM-MS to peptide and protein enrichment strategies allows detection of proteins at the 1-10 ng/mL level in plasma. Other benefits include high molecular specificity, ease of detecting and avoiding interferences, reproducibility of clinical assays, and large numbers of instruments already available in the research community.

CPTC conducted a multi-laboratory study to assess the performance of multiplexed MRM-based assays by spiking 11 signature peptides at 9 concentrations into plasma. Near clinical laboratory reproducibility was achieved in the study with median intra-laboratory coefficients of variation of less than 15 percent, demonstrating that MRM-MS can be reproducible. This work constitutes the first large scale evaluation of MRM-MS technology for quantitation of biomarker candidates in plasma. CPTC also has developed reagents, methods, and datasets that will help other laboratories adopt this technology. Efforts to improve the limit of quantitation and increase the ability to quantify multiple peptides are under way.

## Experimental Design and Biospecimens

Dr. Ransohoff explained that faulty study design and bias are significant barriers to biomarker research. Members were told that: 1) bias is a systematic difference between compared groups, leading to misleading results; 2) can be attributed to instrumentation; for example, mass spectrometry measurements of the same samples done on different days might be different because of spectrometer “drift” occurring over time; and 3) can occur when patient specimens come from different settings (high risk versus screening clinics) or are collected, processed, and handled in different ways. Differences occurring before specimens are received in the laboratory create the most serious problems in current biomarker research. Therefore, specimen collection must be considered part of the study and designed to avoid bias.

The CPTC has started a new study collecting blood specimens from breast cancer screening clinics at 4 CPTC sites prior to diagnosis. The study has been designed with an accrual goal of 2,000 patients (500 breast cancer cases and 1,500 controls are expected). This type of design, called Prospective Collection Before Diagnosis (or PRoBE), helps avoid bias occurring before specimens reach the laboratory. This specimen collection will constitute a high quality resource both for discovery questions and for assessing biomarker detection technology.

### CPTC: Additional Highlights

Dr. Rodriguez described the structure of CPTC. The CPTC portfolio includes the Clinical Proteomic Technology Assessment for Cancer Network (U24); R01s to develop new software tools to facilitate proteomics data analysis and data sharing; R21 and R33 grants for technology development; and a reagents and resources core (funded by a contract). Accomplishments include the development of 26 computational tools and release of public databases to share information. In conjunction with NIST, reagents such as the yeast reference standard and other standards have been released. A monoclonal antibody characterization program at NCI is also being developed at the NCI-Frederick facility and more than 77 monoclonal antibodies are currently available.

He noted that CPTC interacts closely with the U.S. Food and Drug Administration (FDA). Members were told that a workshop was convened by the NCI-FDA Interagency Oncology Task Force and two MACH-510K applications for MRM-based assays and multiplex affinity arrays were developed. CPTC is working with a number of organizations to develop proteomic data sharing policies, similar to those developed by the genomics field.

Future plans are to establish a plasma biorepository of BRCA and normal specimens, and continue discovery and verification studies to evaluate more complex specimens and standardize assays.

### In the discussion, the following points were made:

- < The stability of proteins has been studied in the CPTC and recent tests show that a number of mid- and high-abundance proteins are extremely stable. MRM technology can be used to quantitatively define which proteins are degrading.
- < The MRM-MS technology is not viewed as a replacement for immunoassays, but as a tool to screen proteins at the 100-plex level for cancer relevant proteins to undergo clinical screening.
- < One of the challenges for the field is to move toward non-binder assays and the need to reach low sensitivity for clinical assays. Sensitivity is approaching ng/mL range.
- < Post-translational modifications, such as acetylation and methylation, can be detected using MRM-MS, with the exception of glycosylation.

## **VII. NCI'S FUNCTIONAL PLATFORM TOWARD HIGHLY PERSONALIZED CANCER MEDICINE—DR. JAMES H. DOROSHOW**

Dr. James H. Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), in providing an overview of the NCI's roadmap to personalized cancer treatment, informed members that the critical requirements for the development of personalized cancer treatment include: 1) timely prioritization and dedicated resources for essential biomarker validation studies supported through the Biomarker, Imaging, and Quality of Life (QOL) Studies Funding Program; 2) acceleration of prioritized translational research initiatives for personalized therapy by the Special Translational Research Acceleration Program (STRAP); and 3) support for coordination of clinical/translational research using the Grand Opportunity grant initiative. Dr. Doroshow recognized contributions of the Clinical Trials Working Group (CTWG) and Translational Research Working Group (TRWG) to the development of these programs. He stated that efforts to personalize early phase trials involve a greater focus on proof-of-mechanism early phase clinical trials and the "clinical readiness" of pharmacodynamic assays. These include the adoption of novel approaches to early phase personalized trials, such as a clinical approach to mouse models, and reorganization of the Rapid Access to Intervention Development (RAID) program through elimination of one-third of the pipeline and recent reprioritization of the development of new cancer drugs and biologics.

Members were told that research in cancer pharmacogenomics in relation to therapeutics has provided a profusion of data during the past 10 years, but has not yielded significant results regarding safety, toxicity, or efficacy for patients. Dr. Doroshow illustrated this by an example of tamoxifen pharmacology and the recent recognition that tamoxifen metabolites can exhibit differences in estrogen receptor (ER) binding and inhibition of cell proliferation. Studies found that endoxifen is an equipotent inhibitor of estrogen-stimulated cell proliferation and would bypass pharmacogenetic limitations of tamoxifen on CYP2D6. Since intellectual property rights are not possible for a 30-year-old metabolite despite being a new "drug", the NCI is producing a clinical grade drug to begin the process leading to a Phase I study of endoxifen.

Members were told that the NCI supports the Chemical Biology Consortium (CBC) that integrates chemists, biologists, and molecular oncologists from academic and pharmaceutical organizations, along with synthetic chemistry support, to focus on targets perceived to be "undruggable" and under-represented "orphan" malignancies and to enable a robust pipeline from target discovery through clinical trials for extramural investigators. The CBC will facilitate a much earlier entry point into the drug development platform than previously available, starting with screen development and high-throughput screening of a novel molecular entity. In addition, the Consortium will provide guidance to the NCI in developing the therapeutic pipeline and assisting investigators throughout the United States. Dr. Doroshow also described work on the Tyrosyl-DNA phosphodiesterase 1 (TDP1) protein as a demonstration of the effectiveness of this collaborative approach with high-risk projects. He stated that the NCI will continue work to make the best use of biologic discovery and to engage the private sector in translating this information into new agents for personalized cancer treatment in a timeframe reduced from 12 years to approximately 5–6 years.

### **In the discussion, the following points were made:**

- < The NCI should involve the Centers for Medicare and Medicaid Services (CMS) and the FDA to advance the regulatory and reimbursement climate for molecular diagnostic tests. Staff indicated that the ongoing collaborations between the NCI, FDA, and American Association for Cancer Research (AACR) on biomarkers will lead to a white paper that will provide information to the FDA regarding the extramural community's needs.
- < NCI should utilize the Cancer Centers and Specialized Program of Research Excellence (SPOREs) frozen tumor tissue collection for pharmacodynamic assays, especially for early phase studies.

- < Concerns were expressed about the perception that the NCI is moving toward assuming the pharmaceutical companies' role in drug development, such as the RAID program or CBC. NCI leadership clarified that this is not the case, and that the NCI is striving to provide adequate resources for the academic community.

### **VIII. NCI LISTENS FAQs & As—DR. ROBERT C. YOUNG**

Dr. Young reminded members that the BSA and NCI staff once held open meetings called “NCI Listens” around the country using a “community hall” format at cancer relevant meetings/conferences to hear concerns from the extramural community. After a time, the questions asked at the meetings became standard, and the meetings have now shifted to a computerized access model (online format) through which the public can submit questions. The site also includes other frequently asked questions and answers (FAQs & As).

#### **In the discussion, the following points were made:**

- < The BSA will include on its agenda several times a year a review of the “NCI Listens” Web page to ensure that current concerns in the extramural community about the NCI’s work are fully addressed by specific responses and recommend additional Q&As.
- < The NCI should consider holding occasional teleconferences, web conferences, or other means of live conversation with the extramural community to capture the value that was provided by the original “NCI Listens” meeting format. Staff noted that the NCI does hold sessions for new investigators at national meetings and for specific initiatives.

### **IX. NIH STEM CELL POLICY—DR. IRVING L. WEISSMAN**

Dr. Irving L. Weissman, Director, Stanford University-Comprehensive Cancer Center, informed members that the NIH’s draft guidelines on stem cells include the decision not to fund nuclear transfer-derived pluripotent stem cell lines. Dr. Weissman described several important discoveries resulting from stem cell research, and he recalled the history of federal funding of stem cell research. He noted that President Obama’s speech in March 2009 reflected a change in the Administration’s stance, indicating that the federal government would support such “research when it is both scientifically worthy and responsibly conducted.” Dr. Weissman expressed concern that the proposed NIH guidelines misinterpret President Obama’s message and present barriers to advancing medical science for the health of the American people. Members were encouraged to issue a statement expressing its position on the topic.

#### **In the discussion, the following points were made:**

- < There is no legal ban on implantation but there is a ban on conducting nuclear transfer human stem cell research using federal funds. The research can be conducted by U.S. private companies.
- < There is no consensus among other countries regarding nuclear transfer research in human cells. Several states have passed legislation banning it, while California allows nuclear transfer research.

**Motion.** A motion to prepare a letter addressed to the NIH Director reflecting the Board=s support of removing all constraints to the conduct of scientific research on stem cells, including nuclear transfer stem cells, and the Board=s concern with misinterpretation of President Obama=s intent provided in the draft NIH stem cell guidelines was approved unanimously.

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

**Office of the Director  
Spectral Libraries to Enable Cancer Proteomics (RFP)**

Dr. Christopher Kinsinger, CPTC, explained that a spectral library is a registry of assigned protein MS-MS spectra used as a reference to identify unknown proteins. Advantages of a spectral library are that it: 1) accelerates and improves the identification of low abundant proteins; 2) provides increasing registry of known peptides; 3) becomes an index of assay design; and 4) creates a community wide resource to foster interactions across research groups. Dr. Kinsinger stated that the NIST has been maintaining a spectral library for proteomics for the past four years. Currently, the NIST library lacks spectra from proteins present in cancer tissues. Members were told that this concept supports the collection of high quality tissue samples and generation of cancer-specific protein spectra to be added to the NIST spectral libraries.

Seventy-seven percent of the spectra in the NIST library are from proteins present in plasma. This project will add spectra from proteins in 15 tissue types relevant to cancer (e.g., colon, ovary, breast, lung, and pancreas) and increase the total number of peptides in the NIST library by fifty percent. To this end, the project proposes to partner with the Office of Biorepositories and Biospecimen Research (OBBR) to obtain high quality tissue samples. Partnerships with the Center for Biomedical Informatics and Information Technology (CBIIIT) to facilitate data coordination and dissemination, and the National Center for Biotechnology Information (NCBI) to incorporate into the NIH Peptidome database will also be developed. A contract mechanism will be used to ensure procurement of high quality biospecimens. Augmenting the NIST library with spectra from cancer-relevant proteins will increase the efficiency of the NCI's proteomics effort and enhance biomarker discovery and development.

**Subcommittee Review.** Dr. Richard L. Schilsky, Professor of Medicine, University of Chicago Pritzker School of Medicine, noted that the RFP document stated that only normal tissue will be collected while the presentation stated both normal and cancer tissues will be collected. Members noted that high quality biospecimens are crucial for the success of this effort and more details on specimen collection are needed.

The first year cost is estimated at \$1.7M for 6 awards with a total cost of \$4.8M for 3 years.

**In the discussion, the following points were made:**

- < NCI was encouraged to incorporate signature peptides into the library. Members questioned the usefulness of recombinant proteins.
- < A suggestion was made to use specimens collected by The Cancer Genome Atlas (TCGA) for this project. Staff noted that this is not feasible because of consent and specimen processing issues.
- < In response to concerns about whether these spectra would be relevant for next-generation MS, staff stated that the approach proposed should result in spectra that are reliable across the current three types of mass spectrometers available.
- < NCI should consider conducting a pilot with a limited number of tumors because of concerns about the depth of annotation and quality of tissues from warm autopsies.

**Motion.** A motion to defer the Office of the Director (OD) Request for Proposal (RFP) entitled Special Libraries to Enable Cancer Proteomics was approved unanimously.

**Developing Necessary Reagents to Enable Translation of TCGA and TARGET Discoveries (RFP)**

Dr. Anna Barker, Deputy Director for Advanced Technology and Strategic Partnership, informed members that the Developing Necessary Reagents to Enable Translation of TCGA and TARGET

Discoveries concept was designed to facilitate translation of discoveries generated by large scale cancer genomics programs. Dr. Barker stated that the goals of this pilot program include working with the community to: 1) develop a process to prioritize targets from genomics programs; 2) accelerate functional studies through the development of reagents, protocols, and tools; and 3) provide regular evaluation of the pilot to determine a long term solution.

Members were told that programs such as TCGA and Therapeutically Applicable Research to Generate Effective Treatments (TARGET) have generated large data sets that may permit the identification of relevant signaling pathways, better definition of tumor subtypes (some with correlation to prognosis), and identification of potential druggable targets for several types of cancer. This concept will establish a trans-NCI extramural group that would prioritize submissions from the community regarding potential targets for which reagents (primarily antibodies) are needed. Candidate targets will be vetted for functional relevance and feasibility of reagent production. The prioritization process would be defined by the NCI.

Extramural Target Prioritization Working Group, which would include representatives from the extramural community and NCI program leadership. The final selection of targets would be based on supporting technical evidence, community need, and feasibility. An RFP mechanism was chosen to ensure milestones and deliverables are achieved; facilitate access of the community to reagents and accompanying data; include interested and qualified experts from both the academic and private sectors; and allow re-direction if this approach is deemed ineffective.

**Subcommittee Review.** Dr. Joe Gray expressed the Subcommittee's enthusiasm and concurrence for the concept of improving access to reagents needed to assess function of targets. Dr. Gray stated that members indicated a need for better definition of the reagents, targets, and selection process. Novel targets for which there are no reagents is more justified than developing reagents in commonly researched pathways. The evaluation process also must ensure that the community will effectively use the reagents generated.

The first year cost is estimated at \$2.5M for 4B7 awards with a total cost of \$5M for 2 years.

**In the discussion, the following point was made:**

< Flexibility in matching contractors with targets is needed. NCI plans to use task orders to provide access to a variety of contractors.

**Motion.** A motion to concur on the OD RFP entitled Developing Necessary Reagents To Enable Translation of TCGA and TARGET Discoveries was approved unanimously contingent upon BSA oversight after one year.

**Community Networks Program—Reducing Disparities Through Outreach, Research and Training (CNP-II) (RFA/Coop. Agr.)**

Dr. Sanya A. Springfield, Director, Center to Reduce Cancer Health Disparities (CRCHD), stated that the Community Networks Program (CNP) aims to increase access to and use of beneficial interventions for prevention and early detection of cancer, as well as to identify and develop a cadre of well trained cancer researchers. Dr. Springfield noted that the CNP also emphasizes the dissemination of knowledge to racial and ethnic populations by reaching rural and underserved with mammograms, organizing colorectal Home Health Parties to increase colorectal screenings, and prostate and cervical cancer education. The CNP has trained more than 330 new investigators, published more than 500 peer reviewed papers and made 200 presentations, and has produced over 300 newsletters and websites. The CNP-II will continue to use the community-based participatory research (CBPR) approach to: 1) increase knowledge of, access to, and use of beneficial biomedical and behavioral procedures for cancer and address co-morbidities across the

health care continuum in racial/ethnic minorities and other underserved populations; 2) develop evidence based intervention research; and 3) train a critical mass of researchers using CBPR to reduce health disparities.

**Subcommittee Review.** Dr. William S. Dalton, President and Director, H. Lee Moffitt Cancer Center and Research Institute, said that the Subcommittee recognized the significant work accomplished by the CNP and supported the concept reissuance. Dr. Dalton told members that the Subcommittee also appreciated the well written documentation provided by NCI program staff throughout the review process, particularly regarding the CNP's metrics of success, mechanism of transfer of knowledge, outcome-focused activities, improvement of goals, and published articles. Subcommittee members encouraged the NCI to:

1) strengthen the sustainability of CNP activities; 2) consider randomization of interventions among communities; 3) foster innovative research approaches and to demonstrate the impact of such efforts; and 4) adopt new dissemination strategies.

The first year cost is estimated at \$20.7M for 24 U54 awards with a total cost of \$103.5M for 5 years.

**In the discussion, the following points were made:**

- < Concern about continued support for needs assessments for the next five years was expressed.
- < A focus on new intervention research rather than providing services, such as mammograms, should be encouraged. NCI responded that the CNP II will be required to conduct controlled studies.
- < External experts should be brought in to provide fresh perspectives on research approaches and interventions, including new methodologies, for more effective use of the CNP infrastructure.
- < In response to a concern about a decline in partners who serve ethnic and racial groups, except for African Americans, program staff said the change of focus toward the development of educational interventions with specific groups resulted in the decrease.

**Motion.** A motion to concur on the OD Request for Application RFA)/Coop. Agr. reissuance entitled Community Networks ProgramCReducing Disparities Through Outreach, Research and Training (CNP-II) was seconded and approved with a vote of 27 in favor, 1 nay, and 1 abstention. Staff was advised to take into consideration the members' comments in preparing the RFA document, including the need for enhanced experimental design.

**AIDS Malignancy Clinical Trials Consortium (Letter RFA/Coop. Agr.)**

**Subcommittee Review.** Dr. James K. Willson, Director, Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, informed members that the Subcommittee supported the re-issuance of this concept. Dr. Willson stated that the recent reorganization of the Consortium has resulted in more robust accrual and development of new concepts for clinical trials that currently are being activated in three Human Immuno-deficiency Virus (HIV) associated tumor types. He noted that the closed competition is to help preserve the momentum of the group that has occurred as a result of the reorganization. The 7 core sites and 12 associated sites provide an adequate range of expertise.

The first year cost is estimated at \$4.68M for one U01 award with a total cost of \$26.75M for 5 years.

**In the discussion, the following points were made:**

- < More emphasis should be placed on testing novel therapeutic approaches to AIDS-related malignancies. Expansion to include international sites was strongly supported.

< Concern was expressed about the high cost of accrual. Staff responded that the budget also includes funds to develop international sites and correlative studies.

**Motion.** A motion to concur with the OD Letter RFA/Coop. Agr. reissuance entitled AIDS Malignancy Clinical Trials Consortium was approved with 22 in favor, 3 nays, and 1 abstention.

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

**Subcommittee Review.** Dr. Leland Hartwell indicated that the Subcommittee supported the reissuance. Dr. Hartwell informed members that this program aims to increase cancer research and training among minorities through developing partnerships between cancer centers and minority institutions. Currently, 17 such partnerships are in various stages of development, and the program will seek to maintain 8 to 10 of them in this next phase. With 156 jointly funded grants out of 298 submissions, the program has achieved a 50 percent success rate. Additionally, there have been 389 joint publications, 65 minority faculty who have been recruited to minority institutions, and 13 minority faculty who have been recruited to cancer center institutions. The MI/CCP has trained 236 junior faculty, 83 postdoctoral researchers, 83 medical fellows, 335 graduate students, and 338 undergraduates.

The first year cost is estimated at \$5M for 4–5 U54 awards for a total cost of \$25M for 5 years.

**In the discussion, the following point was made:**

< The program was encouraged to adopt a greater emphasis on translational research. NCI staff noted that several ARRA submissions focus specifically on translational research in cancer that affects minority populations, and provides support to hire new physician scientists.

**Motion.** A motion to concur with the OD Letter RFA/Coop. Agr. reissuance entitled Comprehensive Minority Institution Cancer Center Partnership (MI/CCP) was approved unanimously.

**Division of Cancer Control and Population Sciences  
Transdisciplinary Research on Energetics and Cancer (TREC) (RFA/Coop. Agr.)**

Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences (DCCPS), described the Transdisciplinary Research on Energetics and Cancer (TREC) program, which fosters a multidisciplinary approach to identifying mechanisms that link energy balance and carcinogenesis. Dr. Croyle stated that this has become a pressing issue as the link between obesity and cancer risk becomes clearer. Research performed at TREC centers includes analysis of the effects of gene and environment interactions, diet and physical activity, and animal studies of high glucose diets and dietary glycemic load on cancer risk. Another area of rising interest is the possible relationship between sleep disturbance and obesity; lack of sleep may have a mechanistic impact on metabolic effects and a number of other areas related to obesity.

Members were told that the TREC program held an external review to discuss reissuance of the concept. Based on the report's recommendations, the new RFA will extend participation to investigators outside of the individual TREC centers through the Experts Consultant Committee, establish virtual and technical cores for more efficient use of resources, and expand career development and involvement of junior investigators. As part of the potential impact on policy that TREC may have, the NIH, Centers for Disease Control and Prevention (CDC), and Robert Wood Johnson Foundation have established a strategic partnership called the National Coalition on Childhood Obesity Research (NCCOR). The new initiative will support an open competition for participation, and addition of two new sites was proposed.

**Subcommittee Review.** Dr. Christine Ambrosone, Professor of Oncology and Chair, Department of Cancer Prevention and Control, Roswell Park Cancer Institute, expressed the Subcommittee's enthusiasm for continuation of the TREC centers. Dr. Ambrosone noted that understanding the mechanisms that link

obesity and increased risk for many cancers, as well as poorer survival, is important for development of interventions. The multidisciplinary approach will foster research across basic, population, epidemiologic, and behavioral science and also will contribute to development of public health policies. Research on physical activity, obesity, and diet are important because they each have independent effects on cancer risk.

The first year cost is estimated at \$17M for 6 U54 Transdisciplinary Research Center awards and \$2M for one U01 Coordinating Center award, with a total cost of \$85M for 5 years.

**In the discussion, the following points were made:**

- < The full RFA should have a more explicit focus on cancer.
- < The intent to add two more TREC centers was based on the need for more research breadth in the program, and the increase in scale of the public health problem of obesity and cancer.

**Motion.** A motion to concur with the DCCPS RFA/Coop. Agr. reissuance entitled Transdisciplinary Research on Energetics and Cancer (TREC) was approved unanimously.

**Breast Cancer and the Environment Research Program (BCERP) (RFA/Coop. Agr.)**

Dr. Croyle explained that the NCI co-funds a National Institute of Environmental Health Sciences

(NIEHS) RFA which currently supports four centers through the cooperative agreement mechanism. The research objectives are to: 1) assess normal breast development in the context of environmental exposures; 2) conduct an epidemiological study of the timing of pubertal events in girls; and 3) integrate scientific information to develop effective public health messages. He noted that the RFA is responsive to the Breast Cancer and Environmental Research Act signed October 2008, which authorized \$40M for research and established an interagency coordinating committee.

The BCERP has recruited 1200 girls ages 6 to 8 years at baseline and gathered data on attainment of Tanner stages, menarche, and first ovulation with plans to follow the cohort by supporting three Community and Outreach Training Cores (letter RFA). The next phase also includes the establishment of a Breast Cancer Environment Coordinating Center. Research projects on identifying biomarkers of common exposures, links to genetic polymorphisms, and chemically-induced changes to mammary gland architecture will be funded by R01 and R21 grants through a separate RFA open for competition to the entire research community. Although this is a 6-year NIEHS initiative, the NCI has decided to co-fund the initiative for 5 years, with an option to co-fund in the sixth year depending on progress and productivity.

**Subcommittee Review.** Dr. Kirby Bland informed members that the subcommittee supports the initiative. Dr. Bland stated that the concept represents the only transdisciplinary effort by the NIH to examine puberty as a window of susceptibility for cancer, at which time chemical, biochemical, physical, and genetic factors may influence risk. The proposed research effort is appropriate, particularly given increasing interest in the effects of hormone replacement therapy and environmental endocrine disrupters on breast cancer risk.

The NCI first year cost is estimated at \$3M for 4 U01 awards and 5-6 R01 and R21 awards, with a total cost of \$15M for 5 years.

**In the discussion, the following points were made:**

- < Research funded by this initiative will include analyses of pathways and exposures relevant to breast cancer etiology. Chemical and psychosocial exposures, exposures to environment, stress, and other additional developmental milestones will also be examined.

< The RFA was developed to identify factors that are associated with early pubertal development, which increases breast cancer risk; not follow the cohort through to development of breast cancer.

**Motion.** A motion to concur with the DCCPS RFA/Coop. Agr. reissuance entitled Breast Cancer and the Environment Research Program (BCERP) was approved with a vote of 22 in favor, 1 nay, and 1 abstention.

**XI. ADJOURNMENT-DR. ROBERT C. YOUNG**

There being no further business, the 43<sup>rd</sup> regular meeting of the Board of Scientific Advisors was adjourned at 4:00 p.m. on Monday, 22 June 2009.

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Date

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

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Date

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