

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
NATIONAL INSTITUTES OF HEALTH  
NATIONAL CANCER INSTITUTE  
148<sup>th</sup> NATIONAL CANCER ADVISORY BOARD**

**Summary of Meeting  
December 9, 2008**

**Building 31 C, Conference Room 10  
National Institutes of Health  
Bethesda, Maryland**

**NATIONAL CANCER ADVISORY BOARD**  
**BETHESDA, MARYLAND**  
**Summary of Meeting**  
**December 9, 2008**

The National Cancer Advisory Board (NCAB) convened for its 148<sup>th</sup> regular meeting on Tuesday, 9 December 2008, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, 9 December 2008, from 11:15 a.m. to 3:37 p.m., and closed to the public from 3:37 p.m. to 4:00 p.m. The NCAB Chair, Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, Farmington, CT, presided during both the open and closed sessions.

**NCAB Members**

Dr. Carolyn D. Runowicz (Chair)  
 Dr. Anthony Atala  
 Dr. Bruce A. Chabner  
 Dr. Victoria L. Champion  
 Dr. Donald S. Coffey  
 Dr. Lloyd K. Everson  
 Ms. Kathryn E. Giusti  
 Mr. William H. Goodwin, Jr.  
 Dr. Waun Ki Hong  
 Mr. Robert A. Ingram (absent)  
 Dr. Judith S. Kaur  
 Mr. David H. Koch (absent)  
 Ms. Mary Vaughan Lester  
 Dr. Diana M. Lopez  
 Dr. H. Kim Lyerly  
 Dr. Karen M. Meneses  
 Dr. Jennifer A. Pietenpol  
 Dr. Daniel D. Von Hoff (absent)

**President's Cancer Panel**

Dr. LaSalle D. Leffall, Jr. (Chairperson) (absent)  
 Dr. Margaret L. Kripke (absent)  
 Mr. Joseph P. Torre (absent)

**Alternate Ex Officio NCAB Members**

Dr. Michael A. Babich, CPSC (absent)  
 Dr. Patricia Bray, OSHA/DOL (absent)  
 Dr. Allen Dearry, NIEHS  
 Dr. Diane C. DiEuliis, OSTP  
 Dr. John Krystal, VA  
 Dr. Raynard Kington, NIH (absent)  
 Dr. Peter Kirchner, DOE  
 Dr. Richard Pazdur, FDA (absent)  
 Dr. John F. Potter, DOD  
 Dr. R. Julian Preston, EPA  
 Dr. Dori Reissman, NIOSH (absent)

**Members, Executive Committee, National Cancer Institute, NIH**

Dr. John Niederhuber, Director, National Cancer Institute  
Dr. Anna Barker, Deputy Director for Advanced Technology and Strategic Partnership  
Dr. Kenneth Buetow, Associate Director, Center for Bioinformatics and Information Technology  
Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences  
Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis  
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics  
Dr. Paulette S. Gray, Director, Division of Extramural Activities  
Dr. Peter Greenwald, Director, Division of Cancer Prevention  
Dr. Lee Helman, Scientific Director for Clinical Research, Center for Cancer Research  
Ms. Kathy McBrien, Administrative Resource Center Manager  
Dr. Alan Rabson, Deputy Director, National Cancer Institute  
Mr. Lawrence Ray, Deputy Director for Management and Executive Officer  
Dr. Craig Reynolds, Associate Director, NCI-Frederick  
Dr. Dinah Singer, Director, Division of Cancer Biology  
Dr. Sanya Springfield, Director, Center to Reduce Cancer Health Disparities  
Dr. Robert Wiltrout, Director, Center for Cancer Research  
Ms. Joy Wiszneauckas, Executive Secretary, Office of the Director

**Liaison Representatives**

Ms. Carolyn Aldige, Cancer Research and Prevention Foundation  
Dr. Steven Klein, National Science Foundation  
Ms. Paula Bowen, Kidney Cancer Association  
Mr. William Bro, Kidney Cancer Association  
Dr. Carol Brown, Society of Gynecologic Oncologists  
Ms. Pamela K. Brown, Intercultural Cancer Council  
Ms. Suanna Bruinooge, American Society of Clinical Oncology  
Dr. Yvette Colon, National Cancer Institute, Director's Consumer Liaison Group  
Mr. George Dahlman, Leukemia and Lymphoma Society  
Ms. Brenda Nevidjon, Oncology Nursing Society  
Dr. Margaret Foti, American Association for Cancer Research  
Dr. Robert W. Frelick, Association of Community Cancer Centers  
Dr. Leo Giambarresi, American Urological Association  
Ms. Christy M.P. Gilmour, American Academy of Orthopaedic Surgeons  
Ms. Ruth Hoffman, Candlelighters Childhood Cancer Foundation  
Dr. Lovell A. Jones, Intercultural Cancer Council  
Ms. Rebecca A. Kirch, American Cancer Society  
Dr. Hal C. Lawrence, III, The American College of Obstetricians and Gynecologists  
Dr. W. Marston Linehan, Society of Urologic Oncology  
Mr. David Lofye, Lance Armstrong Foundation  
Mr. Richard Martin, American Society of Therapeutic Radiology and Oncology  
Ms. Margo Michaels, Education Network to Advance Cancer Clinical Trials  
Ms. Christy Schmidt, American Cancer Society  
Ms. Susan Silver, National Coalition for Cancer Survivorship  
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes  
Dr. Robyn Lynn Watson, American Society of Therapeutic Radiology and Oncology  
COL (Ret.) James E. Williams, Jr., Intercultural Cancer Council

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**TUESDAY, DECEMBER 9, 2008****I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF 8 SEPTEMBER 2008 MINUTES—DR. CAROLYN D. RUNOWICZ**

Dr. Runowicz called to order the 148<sup>th</sup> NCAB meeting. She welcomed members of the Board, the President's Cancer Panel (PCP), *ex officio* members of the Board, liaison representatives, staff, and guests. Members of the public were welcomed and invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), National Cancer Institute (NCI), in writing and within 10 days, any comments regarding items discussed during the meeting. Dr. Runowicz reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

**Motion.** A motion was made to approve the minutes of the 8 September 2008 NCAB meeting. The motion was seconded, and the Board unanimously approved the minutes.

**II. FUTURE BOARD MEETING DATES—DR. CAROLYN D. RUNOWICZ**

Dr. Runowicz called Board members' attention to future meeting dates, which have been confirmed through June 2010.

**III. CENTER FOR CANCER RESEARCH—DRS. ROBERT WILTROUT, NATASHA CAPLEN, STEPHAN AMBS, AND TERRY VAN DYKE**

**Introduction.** Dr. Robert Wiltrot, Director, Center for Cancer Research (CCR), said that the Center, which is one of NCI's intramural divisions, integrates basic, translational, and clinical research to make cancer preventable, curable, or chronically manageable. In addition to discovering fundamental mechanisms of biology and cancer, the CCR promotes rapid translation to the clinic; develops innovative technologies; pioneers novel interventions; disseminates its expertise, data, and technologies; and provides a unique environment to cultivate and train future physician-scientists and biomedical researchers. Dr. Wiltrot introduced the speakers: Drs. Natasha Caplen, Genetics Branch; Stephan Ambs, Laboratory of Human Carcinogenesis; and Terry Van Dyke, Mouse Cancer Genetics Program.

**Defining the Functional Cancer Genome Using RNAi-Analysis and Screening.** Dr. Caplen said that RNA interference (RNAi) regulates gene expression relevant to many biological processes. Depending on the source of the original molecules, RNAi can interfere with gene function at the DNA, RNA, or protein level. Artificial RNAs, including short hairpin RNAs (shRNAs) and synthetic small interfering RNAs (siRNA), can be used to test the effects of gene-specific loss of function in mammalian cells. The goal of the Gene Silencing Section is to create a program that will assist investigators wishing to apply RNAi-mediated gene silencing to their research in order to interrogate the function of cancer genes, including those that impact anti-cancer drug activity, and to investigate the role that RNAi plays in the dysregulated gene expression that occurs in cancer cells.

Determining gene function represents a bottleneck in the efforts to improve cancer therapy; use of RNAi can assist in the efficient systematic study of protein function in cancer cells. RNAi can be used to investigate genes with putative or established function; investigate genes present within regions that are amplified or over-expressed in specific cancers; perform allele or isoform specific analysis; and analyze proteins encoding genes with no known function. This approach can be used to target hundreds or thousands of genes in an unbiased manner. The Gene Silencing Section has optimized RNAi delivery to achieve maximum silencing and has silenced over 250 genes.

RNAi screening is being performed to identify genes that reduce cell viability and also to identify genes that enhance or inhibit the efficacy of cancer therapeutics. The Section has screened two breast cancer cell lines to identify and compare molecular targets that influence the viability of tumorigenic breast cancer cells. Because many chemotherapeutics are toxic at higher doses, one goal of this research is to identify targets that interact with the known targets of these drugs in order to enable cell killing at lower dosages. For example, RNAi screening found that silencing MAP3K7 potentiates camptothecin cytotoxicity in breast cancer cells. In addition, genes have been found whose silencing renders ovarian cancer cells sensitive to l-asparaginase, and efforts are underway to extend this finding to brain cancer. This work demonstrates that it may be possible to identify genes that sensitize cancer cells to existing chemotherapeutic drugs, allowing improved efficacy at lower dosages.

RNAi techniques also will be integrated with expression profiling, next-generation sequencing techniques, and systems biology approaches to characterize genes for which there is currently no functional information. The Section also plans to expand its RNAi screening capacity, as NCI will be the lead institute for a trans-NIH RNAi screening program that has defining the functional cancer genome as a goal.

### Questions and Answers

Dr. Jennifer A. Pietenpol, Director, Vanderbilt-Ingram Cancer Center, B.F. Byrd, Jr. Professor of Oncology, and Professor of Biochemistry, Vanderbilt University Medical Center, asked about the prioritization of projects and suggested that the NCI should consider the development and testing of standards of procedures (SOPs) for governance/tiers of review/review committees on smaller scales that eventually could be adopted on a large scale.

In response to a question by Dr. Waun Ki Hong, Professor and Head, Division of Cancer Medicine, Department of Thoracic/Head & Neck Medical Oncology, The University of Texas M.D. Anderson Cancer Center, regarding sensitivity of cells to L - asparaginase, Dr. Caplen explained that an RNAi approach also could be used to identify genes that render cancer cells resistant or sensitive to cancer therapies.

Dr. H. Kim Lyerly, Director, Duke Comprehensive Cancer Center, George Barth Geller Professor of Cancer Research, Duke University Medical Center, asked about the focus on drug interactions and induced resistance to drugs. Dr. Caplen said that induced resistance in initially sensitive cells could be analyzed by performing an RNAi screen using isogenic cell lines with specific genes up- or down-regulated.

**Application of Genomic Profiling to Identify Factors that Contribute to Cancer Health Disparities.** Dr. Ambs provided an update on his research on the contribution of environmental and inherited factors to the excess burden of prostate and breast cancer mortality among African Americans. Reduction of these and other cancer health disparities is one of the best approaches to decreasing the overall burden of cancer in the United States.

Dr. Ambs' study hypothesized that differences in tumor biology may contribute to health disparities because demographic and socioeconomic factors alone do not explain all the variations in cancer incidence and outcome among the various population groups in the United States. His group used large-scale gene expression profiling and analyzed prostate tumors from 33 African-American and 36 European-American patients. They found that 162 genes, including several metastasis-related genes, were expressed differently at a low false discovery rate. Metastasis-promoting genes showed an increased expression in tumors from African American men, and a two-gene tumor signature differentiated the two

patient groups studied.

Additionally, numerous interferon-regulated genes were found to be more highly expressed in tumors of African American patients, which may indicate a viral signature. Along with differences in tumor immunobiology, this fact points to the existence of a distinct tumor microenvironment in the two patient groups. These immune-related differences could disproportionately predispose African American men to tumor progression and may affect the outcomes of therapy.

Dr. Ambs' future research plans involve further examination of tumors in African American patients, specifically immune tolerance and interferon- $\gamma$  signaling, and investigation of the function of the phosphoserine phosphatase-like (*PSPHL*) gene.

### Questions and Answers

Dr. Runowicz requested further details about the clinical parameters of the study. Dr. Ambs confirmed that the investigation controlled for age but not yet for socioeconomic factors.

Dr. Bruce A. Chabner, Clinical Director, Massachusetts General Hospital Cancer Center, and Chief of Hematology/Oncology, Massachusetts General Hospital, asked whether the study had examined co-activators and corepressors in the androgen receptor as the androgen receptor has proven to be an important factor in breast cancer research. Dr. Ambs replied that the study has not examined this issue yet.

Dr. Hong noted the small sample size used in studying *CRYBB2* and *PSPHL* in African Americans and European Americans; he encouraged Dr. Ambs to present his findings to the extramural community, particularly Specialized Programs of Research Excellence (SPORE) investigators focused on prostate cancer, so that the study could be expanded and findings could be strongly validated.

Dr. Judith S. Kaur, Medical Director, Native American Programs, Mayo Comprehensive Cancer Center, and Professor of Oncology, Department of Medical Oncology, Mayo Clinic, suggested that the CCR should look at the whole cancer continuum across a variety of populations. She also asked whether more data would be presented at the Science of Cancer Health Disparities Conference in February 2009.

Dr. John Niederhuber, Director, NCI, asked about differences in whole genome association studies and whether tags or evolutionary evidence of transient viral presence were being sought. Dr. Ambs responded that *8q24* provides one of the best examples in finding a genetic susceptibility locus for cancer and replicating these findings in independent datasets, and these studies also showed that *8q24* is conferring a higher population risk for prostate cancer among African Americans than other race/ethnic groups. He also briefly described research on endogenous retroviruses. Dr. Donald S. Coffey, The Catherine Iola and J. Smith Michael Distinguished Professor of Urology, and Professor of Urology/Oncology/Pathology/Pharmacology and Molecular Science, Johns Hopkins University School of Medicine, asked about the level of prostatic inflammatory atrophy in the samples, and Dr. Ambs indicated that the study has not examined the issue.

**Cancer Models: From Insight to Improved Care.** Dr. Van Dyke said that only approximately 5 of every 100 targeted cancer therapies tested will be approved for use in humans. This situation arises in part because many cancer drugs are tested on xenografts in nude or SCID mice, which does not accurately mimic the crosstalk that occurs between cancer cells and their microenvironment. This system also does not recreate the co-evolution occurring between the cancer cells and the host immune system; the cells used for xenografting have already evolved *ex vivo*. To accurately analyze cancer cell behaviors, analyses

must begin in the earliest stages of cancer development. Mice can be genetically engineered to more accurately study these early stages of tumorigenesis.

A targeted approach has been used to create models of specific human cancers, such as astrocytomas and glioblastomas. These are the most common brain tumors in humans, are highly proliferative and invasive, and have poor prognoses. To model processes occurring early in astrocytoma development, *RB*, *PTEN*, and *K-RAS*, all genes/factors found to be aberrantly inactivated or activated in the development of human cancers, were specifically targeted by engineering recombination sites into regions critical for gene expression or function. Recombination, and thus gene inactivation or upregulation, could be specifically achieved in adult mice by engineering animals to contain a tamoxifen-inducible recombinase allele; administration of tamoxifen triggers the recombination event. This approach was used to specifically inactivate *RB* and *PTEN* and to upregulate *K-RAS*. Inactivation of *RB* and one allele of *PTEN* accelerated progression of the astrocytoma, but not to high grade; activation of *K-RAS* along with *RB* inactivation and complete ablation of both alleles of *PTEN* was needed for high grade glioblastoma multiforme to develop. Human cancer initiates from a single cell, but the putative initiating events occur in all cells of these mouse models. To induce these events in only specific cells, a brain-specific virus can be used to precisely deliver recombinase to only a select cell population in adult animals.

Because *K-RAS* activation was found to be the critical event driving a tumor from low to high grade disease, the many pathways it regulates represent a starting point for analysis of this gene's affect on cancer development and progression. However, few human glioblastomas have *K-RAS* mutations. Instead, downstream tyrosine kinase receptors, such as the epidermal growth factor receptor (EGFR) often are mutated. In the astrocytoma model in which *K-RAS* was upregulated, targeted downregulation of EGFR resulted in massive tumor development and progression to grade 4, including microvascular proliferation. This appears to be the result of a feedback loop between the upregulated *K-RAS* and EGFR ligand. This finding is of critical importance, given the cancer therapies that were developed to inhibit EGFR activity in some tumor types. Loss of EGFR activity in astrocytomas may upregulate platelet-derived growth factor, which may also contribute to tumor growth. A study of non-small cell lung cancer patients treated with an EGFR inhibitor found that those with *EGFR* mutations had a greater likelihood of response to EGFR inhibition, but patients with mutations in *K-RAS* had poorer clinical outcomes when treated with the EGFR inhibitor. Thus, a better understanding of the mutations present in different tumors, and the interactions occurring among these mutations might help to stratify patients for clinical trials and also target therapies more effectively.

These targeted mouse models provide a more precise way to recapitulate the mutations and interactions occurring during the development of cancer. However, broad use of this system in translational research is hindered by a number of issues, including expense, lack of expertise, and regulatory matters. Effective use of this system requires major expertise in cancer mechanisms, pathways, genetics, drug development, and clinical care; thus, a research environment that involves investigators from numerous disciplines is needed. The Center for Advanced Preclinical Studies seeks to facilitate the improvement of preclinical assessment and clinical trial design for effective cancer diagnosis and treatment. The Center will help foster effective interactions among clinicians, physicians, basic research scientists, and drug developers.

## Questions and Answers

Dr. Chabner commented that although these models are useful, they may apply only to a limited subset of tumors that have the same histology and mutations. How this research will affect prediction of efficacy remains to be determined. Dr. Van Dyke agreed that tumors observed in animal models may



resemble human disease but could be genetically different. This research underscores the importance of in-depth analysis of the range of mutations that can occur in tumors. These models may be useful for exploring the genetic signatures of certain subsets of human cancers, particularly those involving common, high penetrance mutations. In addition, gathering data on the range of mutations and the evolutionary processes that result in human tumors is hampered by a lack of patient materials. However, recent work using a well-developed pancreatic cancer model identified four biomarkers present in the serum of pancreatic cancer patients up to 1 year before the cancers development.

Dr. Pietenpol asked about the program's vision to disseminate information quickly and work collaboratively. Dr. Van Dyke explained that part of the work of the Center is to develop a database system that incorporates both preclinical and clinical data, along with the genomic information that soon will be available for numerous cancer types.

In response to a question from Dr. Coffey, Dr. Van Dyke said that although toxicity is affected by genetic background, there are currently no efforts to create models for toxicity differences. However, toxicity could be studied once models with parallel clinical trials have been developed.

#### **IV. CANCER HUMAN BIOBANK (caHUB)—DR. CAROLYN COMPTON**

Dr. Carolyn Compton, Director, Office of Biorepositories and Biospecimen Research (OBBR), NCI, described the NCI's Cancer Human Biobank (caHUB) and addressed concerns raised by the *Ad hoc* Biomedical Technology Subcommittee during its 8 December 2008 meeting. caHUB is intended to fill an infrastructure gap in the United States and be a link to personalized medicine. Based on the Subcommittee's discussion, Dr. Compton noted that: the connection between caHUB and personalized medicine must be clarified; for the successful collection of high-quality specimens and data, all functional issues must be addressed simultaneously; most system requirements are identical, whether or not restrictions exist about the types of specimens collected; the need for this resource must be confirmed by a comprehensive market analysis; and the business model must be sound.

The OBBR embraces a patient-centered vision for all of its initiatives, and the patient's biospecimen is the personalized portion of personalized medicine. The collected biospecimen is analyzed and molecular data are moved through translational research to new diagnostics and therapies; this creates personalized medicine targeted against specific molecular features. Biospecimens will be the basis of the standard of care in the era of molecular and personalized medicine.

The current biobanking system in the United States operates in silos, and banks differ in collection methods, data annotation, patient consent procedures, access policies, materials transfer agreements (MTAs), and supporting information technology (IT) structures. These differences create a wide variation in the quality of both specimens and data used for research.

The NCI developed the National Biospecimen Network Blueprint in 2003, and its principles provide the basis on which caHUB is founded: standardized biospecimen collection and distribution procedures; standardized datasets; integrated IT; standardized consent and MTA practices; transparent governance; and large, scientifically designed specimen sets. The importance of standardized specimens and a national biospecimen resource has been cited widely over the past several years. Several other nations already have programs similar to caHUB in place.

The National Biospecimen Network Pilot study was carried out in 2005–2006, and revealed numerous challenges posed by process variation among 11 prostate cancer SPORE sites. The pilot was terminated due to the inconsistency among sites and the fact that the business model for the pilot was

inadequate, but resulted in the creation of the guidebook “NCI’s Best Practices for Biospecimen Resources.” The Cancer Genome Atlas (TCGA) project also serves as a case study in biospecimen challenges and solutions. From TCGA, the NCI learned that biobank inventory dropout rates can be as high as 95 to 99 percent, and the molecular quality control (QC) failure rate was approximately 30 percent. The quality of existing samples is highly overestimated, and collection of normal samples is not routine. Once prospective patient consent and tissue collection, standard operating procedures, and training and education in all aspects of the process were instituted, however, TCGA became a proven success. The lessons learned are directly applicable to caHUB, and demonstrate that specimen challenges can be met; however, the current system is inadequate.

Key concepts for caHUB include: scientifically designed collection strategies, standardized processing, centralized QC and a centralized source of normal specimens, and provision of tools and resources for the broader research and medical community. caHUB is now in the early planning phase of market research, and approval for FY 2009 has been requested. In-depth interviews were conducted with 22 respondents in July and August of 2008, and 727 participants completed an online survey in October of 2008. Initial results show that researchers are working in silos, but the reaction to a national biobank has been 75 percent positive. High quality biospecimens allow the product validation of new treatments and diagnostics not otherwise possible, because original results can be reproduced, which allows the product to be fully tested and approved for market. The U.S. Food and Drug Administration (FDA) has noted that the biggest problem faced in creating submissions for new diagnostics is access to well-annotated human specimens.

The OBBR will convene a number of working groups with a variety of domain expertise during the caHUB planning phase. The planning phase will last throughout the next year and require approximately \$1.2 M. From that point forward, caHUB will not be looking solely to the government for financial support, but plans to engage the resources of industry and philanthropy to be effective.

## Questions and Answers

Dr. Coffey affirmed the need for such a system, but cautioned that its development must be carefully planned due to its high cost and the number of hospitals and pathologists it will serve. Dr. Chabner agreed that establishing a specific need for caHUB is important. This would require a broader survey of NCI grantees about their pathology needs, because the number of respondents was low on the previous survey and included 50 percent nonlaboratory staff. More information is needed on whether the need is simply for tissue samples or for samples from specific clinical trials, which would be very important in establishing individualized medicine. Additionally, before caHUB goes beyond the survey process, the issue of providing samples to industry should be addressed.

Dr. Victoria L. Champion, Associate Dean for Research, Mary Margaret Walther Distinguished Professor of Nursing, Center for Research & Scholarship, Indiana University School of Nursing, stated that because cancer is a disease of biology, behavior, and the environment, the development of the databases should be approached in a broad manner. Databases should provide additional information that may inform why certain tissues react as they do to certain drugs. This issue may be beyond the scope of the current discussion, but personalized medicine is more than genomics; it is personalized in terms of behavior, culture, and environment as well.

Ms. Kathryn Giusti, CEO and Founder, Multiple Myeloma Research Foundation, Inc., noted that the Subcommittee had raised four issues to be addressed to streamline the process so that the caHUB working groups would have a cleaner proposal: 1) Who will be the provider of the tissue? 2) Who is the user of the tissue (e.g., academic settings will seek different types of tissue than industry)?; 3) What are

the scientific problems to be solved? (e.g., genomics, proteomics, and biomarkers); and 4) What is the funding model?

Dr. Lloyd K. Everson, Vice Chairman and Member of the Board of Directors, US Oncology Incorporated, noted that approximately 80 percent of the trials conducted in his oncology network are linked to some genomic/proteomic marker identification mechanism, but the key missing link and key cost factor is the database. A longitudinal electronic medical record (EMR) database is needed so that markers can be linked to the history of the patient. He added that the American College of Surgeons' (ACS) Commission on Cancer's (COC) National Cancer Database (NCDB) is excellent for its purpose, but for this project it may not be sufficient. Dr. Compton noted that the caHUB team had met with NCDB leadership to discuss working with the database. The NCDB is a unique resource in the United States because of its requirement for COC approval of standard of care delivery; it also has data on 80 percent of all cancer patients in the United States, and the data currently are unavailable to the research community.

Dr. Anthony Atala, Director, Wake Forest Institute for Regenerative Medicine, and Professor and Chairman, Department of Urology, Wake Forest University School of Medicine, asked about caHUB's plans to add additional centers and tumor types. Dr. Compton explained that the initial plan was to build on existing relationships with cancer centers to collect additional tumor types; the NCI Community Cancer Center Project (NCCCP) is a pilot to study the feasibility of bringing community cancer centers into the research enterprise to allow their patients to be entered into clinical trials, and to allow the centers to collect biospecimens in a setting with much less competition. Dr. Anna D. Barker, Deputy Director for Advanced Technology and Strategic Partnership, added that in speaking to TCGA's steering committee, it became apparent that next generation sequencing will provide comprehensive data on the genome in a very short period of time; therefore, a centralized biospecimen bank will have to be created, because cancer research activities will have to shift. New approaches for translational genomics are needed, and the infrastructure must be built within the timeframe that technology dictates.

## **V. DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS—DRS. JOSEPH F. FRAUMENI, JR., AND STEPHEN CHANOCK**

**Introduction.** Dr. Joseph F. Fraumeni, Jr., Director, Division of Cancer Epidemiology and Genetics (DCEG), said that it has long been recognized that the environment plays a large role in cancer incidence. Research priorities in cancer etiology have shifted through the decades from oncogenic viruses (1960s), to chemical carcinogens from occupational and environmental exposure (1970s), to lifestyle practices (1980s), and to the contribution of inherited high-penetrant genes (1990s). More recently, new genotyping platforms, which enable genome-wide association studies (GWAS), have made it possible for epidemiologists to identify the low- and medium-penetrant gene variants that are common in the general population and may have a substantial impact on the burden of cancer, especially through interactions with environmental factors.

At the NCI, new genomic advances and technologies have shifted the emphasis from candidate gene searches to systematic genome-wide scans through the Cancer Genetic Markers of Susceptibility (CGEMS) project. CGEMS is designed to conduct large-scale association studies with staged replication strategies that include intramural/extramural consortia of groups with cohort and case-control studies coordinated by DCEG in conjunction with the Division of Cancer Control and Population Sciences (DCCPS). Its subsequent activities include resequencing and fine-mapping of genomic loci to narrow the search for inherited genetic variants as well as downstream research with CCR and other scientists that range from functional studies to the study of germline versus somatic changes, pharmacogenomics, gene-environment interactions, risk prediction models, and clinical applications. GWAS findings are posted rapidly through the caBIG database.

Dr. Fraumeni described the establishment of the NCI Consortium of Cohorts, which currently includes 37 population cohorts with nearly 4 million individuals, noting that GWAS projects have enormously increased our understanding of the genetic background to cancer and other diseases. He then introduced Dr. Stephen Chanock, Chief, Laboratory of Translational Genomics, DCEG.

**Genome-wide Association Studies.** Dr. Chanock described the progress of the GWAS program, particularly the relationship between the intra- and extramural epidemiologic communities. He reminded members of milestones in human genomics and disease susceptibility, including achievements of the Human Genome Project and International HapMap Project, as well as the assembly of dense markers for association studies, the development of robust genomic analysis technologies, and GWAS with replication. The basic principle of genetic association studies is to examine groups of unrelated individuals who have or do not have the disease of interest and determine whether differences exist in the distribution of the genetic variances that associate with disease risk. Genetic association testing hence has focused initially on finding markers in the genome that have strong association signals. GWAS is working to discover new “candidate genes;” explore genes and pathways through etiology, gene-environment lifestyle interactions, and “druggable” targets; and establish the utility of genetic markers for risk prediction that might influence individual or public health decisions.

GWAS research includes studies to identify genetic markers for prostate and breast cancers, diseases that pose public health problems: lifetime incidence rates are 1 in 8 men for prostate cancer and 1 in 9 women for breast cancer. The initial investigation has analyzed DNA from the NCI PLCO and Nurses’ Health long-term studies with large-scale follow-up. Based on the findings, next steps include fine-mapping and functional studies to validate plausible variants and eventual test in the clinic. In addition to age, ethnic background, and family history, which have been associated with prostate cancer risk, GWAS in prostate cancer have identified 16 regions of the genome as risk factors, with *MSMB*, b-microseminoprotein, and a region of chromosome 10 of particular interest. Work in breast cancer has focused on polymorphisms in *FGFR2*, *TNRC9*, and *8q24*; risk conferred by these variants is modified by the estrogen receptor status of the breast tumor. Additionally, GWAS was used to identify cancer susceptibility loci in the *8q24* region for both prostate and breast cancers; resequencing analysis of variants has suggested that there may be more than one variant important in this area, and further genotyping is warranted to nominate SNPs for functional analysis. Initial observations on *8q24* prostate cancer susceptibility include: all common variants are identified within a 136 kb region; two SNPs highly correlated with rs6983267 are associated with prostate, colon, and ovarian cancers; 43 SNPs and two insertions/deletions highly correlated with rs4242382 are associated with prostate cancer in Caucasian men.

Dr. Chanock said that DCEG has a strong commitment to GWAS, such as CGEMS and supports ongoing work in breast, prostate, lung, bladder, kidney, and upper gastrointestinal cancers, as well as non-Hodgkin lymphoma (NHL). Studies are also underway to identify risk variants in brain and testicular tumors, as well as melanoma. Future activities include: mapping loci to identify the most promising variants for biological investigation; conducting functional analysis of variants to provide plausibility and explore pathways; developing new GWAS for outcomes; and conducting GWAS for etiology in comparable environmental exposures to further understand the role of gene-environment interactions. GWAS findings should be studied in terms of risk assessment, pharmacogenomics, value for public health and personal decisions, and comparisons of new and old paradigms.

## Questions and Answers

Dr. Coffey asked about the best case scenario for personalized medicine when less than 50 percent of identical twins have the same cancer. Dr. Chanock replied that genetic determinism can be a dangerous concept; the gene-environment interaction is a key component that will require careful examination, particularly from the perspective of cancer prevention.

Dr. Hong asked about work with mitochondrial SNPs as well as coordination of genetic variations to detect through the analysis and same genetic changes of tumor tissue. He also wondered about the cost of human analysis. Dr. Chanock said that a comprehensive view of mitochondrial DNA and SNPs is nearing completion, and several mitochondrial variants appear interesting. Work on the relationship of the germline variation to somatic alterations from microarrays continues and Dr. Chanock shared an example of this with amplification in *8q24*. The cost of the analysis continues to decrease as new technologies are developed.

Dr. Niederhuber asked about the process of sorting relationships between sites and specific cancers and noted that higher mathematics might be able to write equations to assist with this. Dr. Chanock agreed this could be helpful and noted that large sample sizes also are needed. Dr. Niederhuber wondered about the interest in the community about this, and Dr. Coffey referred to an article in *Nature* that pointed to this association work as a future direction. Dr. Barker commented that relationship issues are still redefining what a gene is and that the bioinformatics field should be integrated better as an organic part of the solution.

## VI. CLOSED SESSION—DR. CAROLYN D. RUNOWICZ

*“This portion of the meeting was closed to the public in accordance with the provisions set forth in Sections 552b(c) (6), Title 5 U.S. code and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2).”*

Members were instructed to exit the room if they deemed that their participation in the deliberation of any matter before the Board would be a real conflict or that it would represent the appearance of a conflict. Members were asked to sign a conflict-of-interest/confidentiality certification to this effect.

There was a review of intramural site visits and tenured appointments, committee discussions, and recommendations. There also was a discussion of personnel and proprietary issues. Members absented themselves from the meeting during discussions for which there was potential conflict of interest, real or apparent.

## VII. ADJOURNMENT—DR. CAROLYN D. RUNOWICZ

Dr. Runowicz thanked all of the Board members, as well as all of the visitors and observers, for attending.

There being no further business, the 148<sup>th</sup> regular meeting of the NCAB was adjourned at 4:00 p.m. on Tuesday, 9 December 2008.

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Date

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Carolyn D. Runowicz, M.D., Chair

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Date

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Paulette S. Gray, Ph.D., Executive Secretary