DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
150TH NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
June 11, 2009

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

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
Summary of Meeting
June 11, 2009

The National Cancer Advisory Board (NCAB) convened for its 150th regular meeting on 11 June 2009, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Thursday, 11 June 2009, from 8:30 a.m. to 3:15 p.m., and closed to the public on Thursday, 11 June 2009, from 3:30 p.m. to 5:00 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 (absent)
Dr. Bruce A. Chabner
Dr. Victoria L. Champion
Dr. Donald S. Coffey
Dr. Lloyd K. Everson (absent)
Ms. Kathryn E. Giusti
Mr. William H. Goodwin, Jr. (absent)
Dr. Waun Ki Hong
Mr. Robert A. Ingram
Dr. Judith S. Kaur
Mr. David H. Koch
Ms. Mary Vaughan Lester
Dr. Diana M. Lopez
Dr. H. Kim Lyerly
Dr. Karen M. Meneses
Dr. Jennifer A. Pietenpol
Dr. Daniel Von Hoff

President=s Cancer Panel
Dr. LaSalle D. Leffall, Jr. (Chairperson) (absent)
Dr. Margaret L. Kripke
Mr. Joseph P. Torre (absent)

Alternate *Ex Officio* NCAB Members
Dr. Michael A. Babich, CPSC
Dr. Patricia Bray, OSHA/DOL
Dr. Michael Kelley, VA
Dr. Lawrence A. Tabak, NIH (absent)
Dr. Peter Kirchner, DOE (absent)
Dr. Steven Kleeberger, NIEHS
Dr. Richard Pazdur, FDA
Dr. John F. Potter, DOD
Dr. R. Julian Preston, EPA (absent)
Dr. Michael Stebbins, OSTP
Dr. Elizabeth Whelan, NIOSH

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. Jim Dickens, Acting 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
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
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. Steven Klein, National Science Foundation
Dr. Hal C. Lawrence, III, The American College of Obstetricians and Gynecologists
Dr. W. Marston Linehan, Society of Urologic Oncology
Mr. Adam Clarke, 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

TABLE OF CONTENTS

THURSDAY, JUNE 11, 2009

THURSDAY, JUNE 11, 2009

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF 3–4 FEBRUARY 2009 MINUTESCDR. CAROLYN D. RUNOWICZ

Dr. Runowicz called to order the 150th 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.

Dr. Runowicz congratulated NCI leaders for recent awards: Dr. Anna D. Barker, NCI Deputy Director, Advanced Technology and Strategic Partnership, received the American Association for Cancer Research (AACR) Margaret Foti Award for Leadership and Extraordinary Achievements in Cancer Research; and Dr. Joseph Fraumeni, Jr., Director, Division of Cancer Epidemiology and Genetics (DCEG), received the AACR Award for Lifetime Achievement in Cancer Research.

Motion. A motion was made to approve the minutes of the 3–4 February 2009, NCAB meeting. The motion was seconded, and the Board unanimously approved the minutes.

II. FUTURE BOARD MEETING DATESCDR. CAROLYN D. RUNOWICZ

Dr. Runowicz called Board members' attention to future meeting dates, which have been confirmed through 2011.

III. NCI DIRECTOR'S REPORT DR. JOHN NIEDERHUBER

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

American Recovery and Reinvestment Act of 2009. Members were reminded that the ARRA, which President Obama signed into effect on 17 February 2009, allocated $10.4 B to the NIH, of which $1.267 B went to the NCI, and the remaining total to other Institutes and Centers (ICs) ($6.133 B), extramural construction ($1 B), NIH construction ($500 M), shared instrumentation ($300 M), comparative effectiveness research ($400 M), and the NIH Office of the Director (OD) ($800 M). The ARRA allocates a significant amount of money to information technology (IT), and members were reminded that the NCI has been at the forefront of developing ways to connect science, clinical trials, and patient care databases.

Dr. Niederhuber said that the NCI is working to meet the ARRA's goal of maintaining and increasing jobs while funding the best new science, using models to ameliorate funding issues that might result from ARRA "one-time" dollars, and investing in science that will make a difference for patients. The NCI support for individual investigators is projected to be at the 25th percentile for fiscal year (FY) 2009: the Research Project Grant (RPG) payline is estimated at the 16th percentile, increased to the 18th percentile through 4-year grants funded from ARRA that will be followed by appropriated dollars, and further increased to the 25th percentile through a mixture of 2-year and 4-year grants that are supported by ARRA funds for the initial 2 years. Members were told that 40 percent of eligible RPGs (156 of 384) have been funded to date. The NIH received approximately 20,000 ARRA Challenge Grant applications, of which nearly 4,400 are cancer related, and approximately 2,500 Grand Opportunity grants, of which more than 550 are cancer related. Nearly 50 ARRA funding announcements have been posted and made available to the community to apply for NCI support. Dr. Niederhuber noted that grants that are ready to be awarded

are submitted weekly through the NIH to the White House, and most grants are officially awarded about 2 weeks after their inclusion on the weekly list. Members also were informed that ARRA funds must be spent by the end of FY 2010, and that the NCI has grant specialists assigned to work exclusively on ARRA grants.

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 $4.968 B, reflecting an increase of $138 M (2.9%) over the FY 2008 level. He reviewed the policies that the NCI has followed in revising its budget and noted that the Institute will award more competing RPGs than in FY 2008 (from 1,284 to 1,412), meeting the NIH target for competing new investigator R01 awards. In addition, there is a 3 percent increase for Type-2 grants and a 5 percent increase for grants recommended for up to seven modules, as well as a reduction of approximately 17 percent in the amount of funding requested for Type-1 grants. The NCI's success rate remains steady for both competing RPGs and first-time investigator awards, with an average cost per grant of $366,000 and $91,000, respectively. The FY 2010 President's Budget proposes $5.15 B for the NCI, representing an increase of $181 M (3.5%).

Dr. Niederhuber reported that new NCI-designated cancer centers include the University of Maryland Marlene and Stewart Greenebaum Cancer Center, the Medical University of South Carolina Hollings Cancer Center, and the Emory University Winship Cancer Institute.

Trans-NIH Cancer Strategic Plan. Members were informed that the President proposes to invest more than $6 B for cancer research across the NIH, reflecting the first year of an 8-year strategy to double cancer research by FY 2017. Drs. Niederhuber and Stephen Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), were appointed by the NIH to chair a committee to develop the Trans-NIH Cancer Strategic Plan. All ICs that conduct cancer research (24 of 27 NIH ICs) have submitted information, and the report is being prepared for submission to the NIH on 24 June.

Questions and Answers

Mr. David H. Koch, Executive Vice President, Koch Industries, requested clarification about the awarding of the ARRA funds. Dr. Niederhuber said that the Act's goal is to protect and increase jobs; in adherence to policies of the Office of Management and Budget (OMB), the NCI is awarding and reporting ARRA-supported funding separately from the operating budget. Dr. Bruce Allan Chabner, Clinical Director, Massachusetts General Hospital Cancer Center, and Chief of Hematology/Oncology, Massachusetts General Hospital, asked whether special consideration is being given to new grantees in the adjustment of the payline to the 18th and 25th percentiles. Dr. Niederhuber affirmed this, further explained that NCI leadership believed new investigators needed more than 2 years, and agreed to commit appropriated dollars for the third, fourth, and fifth years. He said that administrative supplements are used to support existing grants but that ARRA funds cannot be used for such grants. In response to a question by Mr. Koch, NCI staff clarified that new investigators are receiving up to $1 M, with the average grant totaling $300,000 per year.

Dr. Runowicz applauded Dr. Niederhuber and NCI staff for their hard work in administering appropriations and ARRA monies. Dr. Niederhuber acknowledged the temporary assistance of NCI retired personnel in covering some of the additional work.

Mr. Koch asked about the criteria required for a medical center to become an NCI-designated cancer center. Dr. Niederhuber replied that a variety of components are considered in a rigorous review, including resource commitments from the university, medical school, or hospital, and the quality of the organization's programs during the past 5 years.

Dr. Chabner complimented the NCI on managing the ARRA funding and applauded the emphasis on individual investigator-initiated research. He voiced concern about the role of the cancer centers program given the recent shifts in the NCI portfolio. Dr. Niederhuber recognized the challenges faced by the centers, which rely heavily on endowments that have shrunk in the current economy, and commented that nearly 70 percent of allocated ARRA funds are going to investigators who are based in the cancer centers. He added that supplemental funds can be provided to assist core support grants, including for staff recruitment, such as minority investigators, but that ARRA funds must be distributed according to the mandates of the ARRA bill. Dr. Niederhuber said that, although not as readily seen, the ARRA funds are addressing disparity issues and providing greater support for continued fellow and postdoctoral fellow positions in response to the limited academic or other career opportunities.

Dr. H. Kim Lyerly, Director, Duke Comprehensive Cancer Center, and George Barth Geller Professor of Cancer Research, Duke University Medical Center, asked about the future of comparative effectiveness research (CER) in the NCI's portfolio. Dr. Niederhuber answered that the NCI has incorporated CER in its long-term plans for many years, particularly with knowledge management and the relationships built between large databases and health care systems; CER is a vehicle that Congress can use to transform U.S. health care into a knowledge-based system. He said that, in the new era of medicine, new endpoints could be determined by focusing CER resources to better understand and make therapeutic solutions with new definitions of disease for the cancer patient, rather than be limited to cancer itself. Dr. Robert T. Croyle, Director, Division of Cancer Control and Population Sciences (DCCPS), added that, in the cancer domain, the NCI has developed a strong incidence surveillance system with data linked to Medicare claims data; scientific opportunities also exist in other domains relevant to CER, including evidence synthesis and implementation, guidelines development, and health care quality improvement in cancer, as well as molecularly informed CER.

IV. PRESIDENT'S CANCER PANEL DR. MARGARET L. KRIPKE

Dr. Margaret Kripke, President's Cancer Panel (PCP, the Panel), thanked the NCAB and offered PCP Chair Dr. LaSalle Leffall's regrets that he could not be present at the meeting. Dr. Kripke noted that Lance Armstrong was no longer a Panel member and had not yet been replaced. The mission of the PCP is to monitor the development and execution of the National Cancer Program (NCP) and report directly to the President. Dr. Kripke explained that the National Cancer Program encompasses NCI's work as well as additional research, advocacy, and delivery in cancer. The PCP should notify the President immediately of any delays or impediments to the National Cancer Program's progress in reducing the cancer burden.

To monitor the NCP, the PCP closely examines one segment of the program annually. The PCP's 2008–2009 meeting series, on which its forthcoming Annual Report is based, studied the role of environmental factors in cancer. Themes covered in this meeting series included: industrial, manufacturing, and agricultural exposures; indoor/outdoor air pollution and water contamination; and nuclear fallout, electromagnetic fields, and radiation exposure. Possible outcomes of the report may include determination of the status and role of regulatory agencies responsible for monitoring environmental hazards, and identification of research needs and potential new areas of collaboration among federal agencies. The annual report, to be released in the fall of 2009, will increase public awareness of environmental and occupational hazards and cancer risk, and provide recommendations for reducing cancer risk from environmental exposures to pollutants and regulating toxic and potentially hazardous chemicals and materials. Dr. Kripke noted that the impact of environmental factors in cancer incidence is not known; this is the most important finding in the meeting series and report. The often-quoted statistic that environmental cancers account for approximately 6 percent of the cancer burden was drawn from research that excludes secondhand smoke and many other factors known to be important in environmental cancers.

The PCP's next meeting series will be entitled "America's Demographic and Cultural Transformation: Implications for the Cancer Enterprise." The series will address: the implications for U.S. cancer trends as the proportions of ethnic subpopulations increase; determination of biologically based differences, if any, among ethnic groups in clinical presentation or response to cancer treatment that justify differences in the type and intensity of care; determination of whether clinical encounters differ across ethnic groups; and examination of the extent to which patients and providers contribute to health disparities. The information learned from this series might determine a need to revise screening guidelines to reflect the medical realities of cancer in particular ethnic groups, and likely will address cultural competency among health care providers. The PCP also is drafting a summary of the major challenges to progress in cancer treatment and prevention based on the knowledge gleaned from its past decade of work; Dr. Kripke noted that this may be available at the next NCAB meeting.

Questions and Answers

Dr. Runowicz thanked Dr. Kripke and asked about the outcome of the PCP's previous report, *Maximizing Our Nation's Investment in Cancer: Three Crucial Actions For America's Health*. Dr. Kripke noted that the report identifies challenges in cancer prevention and treatment that need to be addressed.

Mr. Koch asked whether the effect of chemicals' concentration correlation to cancer would be considered in the PCP's report. Dr. Kripke responded that concentration is taken into account when evaluating chemicals' carcinogenic potential to determine their risk/benefit ratio. She noted that in the United States, chemicals are regulated when they are found to be harmful, whereas some other countries, especially in Europe, do not allow chemicals on the market until their safety has been demonstrated.

Ms. Kathryn Giusti, CEO and Founder, Multiple Myeloma Research Foundation, Inc., noted that Lance Armstrong's presence on the PCP had helped to publicize its work, and asked whether Joe Torre's pending appointment to the Panel was still under consideration. Dr. Kripke responded that the new administration would have to make the appointment, and that it likely was not a high priority so may be further delayed.

Dr. Karen M. Meneses, Professor and Associate Dean for Research, University of Alabama at Birmingham School of Nursing, asked if the next series of meetings had been scheduled. Dr. Kripke replied that they are in the process of being scheduled, and the PCP welcomed suggestions on locations and topics from NCAB members.

Dr. Donald S. Coffey, The Catherine Iola and J. Smith Michael Distinguished Professor of Urology, Johns Hopkins University School of Medicine, noted that it has been known for 50 years that the number of breast and prostate cancer cases in Chinese immigrants increases approximately tenfold when they move to the United States, but the reason for the increase is not known. He asked if the environmental factors that the PCP had been studying offer any insight into this question, and additionally whether a study of body flora, which vary significantly by country, and their effects on processing carcinogens and protective agents had been considered. Dr. Kripke responded that lifestyle factors were not being considered for the report, only environmental factors, but that some fundamental genetically based differences may come to light in the upcoming meeting series. Dr. Victoria L. Champion, Associate Dean for Research and Mary Margaret Walther Distinguished Professor of Nursing, Center for Research & Scholarship, Indiana University School of Nursing, commented that the public's frequent sanitization of their surroundings may have an effect on bacterial flora in the environment.

Dr. Judith S. Kaur, Medical Director, Native American Programs, Mayo Comprehensive Cancer Center, and Professor of Oncology, Mayo Clinic, advised that when addressing biologically based differences between ethnic groups and resulting differences warranted in the type and intensity of care

provided, it will be important to see how various populations view the move from standardized care to individualized care. Educating the public about this also is important. Dr. Kripke noted that it already is known that different populations view the problem of cancer very differently, and acceptance of the diagnosis varies substantially across different groups depending on background, religion, and other factors.

Dr. Michael A. Babich, Directorate for Epidemiology and Health Sciences, Consumer Product Safety Commission, asked if the PCP planned to receive input from any regulatory agencies on the environmental causes of cancer before developing its recommendations. Dr. Kripke responded that regulatory agency staff presents testimony to the PCP at open meetings of the panel to offer insight for the report.

Dr. Chabner noted that tobacco is the greatest cause of environmental carcinogenesis and asked, because the new administration will be more active in regulating tobacco, if the PCP would revisit the topic.
Dr. Kripke responded that the subject would be revisited in the white paper on challenges she had mentioned; it was considered in the previous report, and the PCP would continue to publicize the issue.
Dr. Runowicz suggested that the NCAB should revise and resubmit its letter on the topic once the new presidential appointments to the NIH are made.

V. LEGISLATIVE UPDATE MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), reported on appropriations and several new bills that were introduced, and provided information on Congressional priorities for 2009.

Appropriations Status. The President's Budget was released May 7, 2009, and contains approximately $30.8 B for the NIH and $5.15 B for the NCI. Approximately $6 B also has been allocated for cancer research to be conducted throughout the NIH. Hearings were held in the House of Representatives on March 26, 2009, and in the Senate on May 21, 2009. Representative David Obey (D-WI), the Chair of the House Appropriations Committee, stated that the Labor HHS bill would be voted on by the subcommittee July 8, the full committee on July 14, and the House July 24. Both he and Senator Daniel Inouye (D-HI), Chair of the Senate Appropriations Committee, have stated that their goal is to have all of the respective appropriations bills completed by the August recess.

Legislation of Interest. Several bills of interest to the NCAB have been introduced. The 21st Century Cancer Access to Life-Saving Early Detection Research and Treatment (S. 717), also referred to as ALERT, was introduced by Senators Edward Kennedy (D-MA) and Kay Bailey Hutchison (R-TX), and has been referred to the Senate Committee on Health, Education, Labor, and Pensions. ALERT was introduced to enhance and improve the cancer research conducted and supported by the NCI and NCP, increase focus on biospecimens, and enhance cancer research reporting. The Comparative Effectiveness Research Act (H.R. 2502), introduced by Representative Kurt Schrader (D-OR), would establish a non-profit corporation (the Health Care CER Institute) to study the effectiveness of various health care plans, and create a CER trust fund that would impose fees on self-insured plans. The CER Act also would require that research be peer-reviewed, Center for Medicare and Medicaid Services data be made available, and that the newly formed Institute disseminate findings. Representative Anna Eshoo (D-CA) and Senator Ron Wyden (D-OR) introduced the Healthy Americans Act (H.R. 1321; S. 391) to provide affordable, guaranteed private health coverage. The Family Smoking Prevention and Tobacco Control Act (H.R. 1256) passed the House on April 2, and was subject to Senate debate beginning on June 1, 2009; the President has committed to sign the Act once passed.

Congressional Priorities 2009. Ms. Erickson noted that the priorities of the 111th Congress will be to pass the aforementioned appropriations bills and health care reform. There are five Committees (two

in the Senate and three in the House) working on health care reform, which will require a great deal of time and energy.

Questions and Answers

Mr. Koch asked Ms. Erickson to note the key features of the tobacco bill. She responded that the bill's primary objective is to give the U.S. Food and Drug Administration (FDA) the authority to regulate tobacco, but that would not include the authority to ban tobacco. Dr. Croyle further noted that the bill would give FDA the authority to require product ingredient disclosure in tobacco products, require more graphic and visible warning labels, and restrict marketing, particularly to youth, by banning sponsorship of concerts and events. FDA also could regulate nicotine content in tobacco, short of banning nicotine. The implications of modifying nicotine levels are not fully understood, so the NCI has sponsored some workshops to address the issue. There likely will be debate concerning what the nicotine levels should be, and what the implications of those levels are. The bill, if passed, likely would be the largest, most high impact cancer control intervention in U.S. history.

VI. LUNG CANCER PROGRAM DRS. GUISEPPE GIACCONE, NEIL CAPORASO, AND PHILLIP DENNIS

Dr. Guiseppe Giaccone, Chief, Medical Oncology Branch, opened the presentation on the NCI Lung Cancer Program by introducing himself and the other speakers: Drs. Neil Caporaso, Senior PI, Genetic Epidemiology Branch, DCEG; and Phil Dennis, Senior PI, Medical Oncology Branch.

Dr. Caporaso reminded members that lung cancer is the leading cause of cancer death in the United States, accounting for more cancer mortality than the five next most prevalent cancers combined. Screening and treatment are challenging, and the 5-year survival rate for lung cancer is low. Lung cancers may have an important genetic component; relatives of people with lung cancer are at elevated risk for this cancer (after controlling for other risk factors), pedigrees suggest a familial component, and pharmacogenetic work shows genetic control of differential metabolism of a variety of chemicals and toxins. Lung cancer presents a paradigm for studying the genetics of a complex disease and for understanding how genes and environment interact to cause cancer, given that the dominant environmental cause of lung cancer—smoking—is well known. Smoking also is a clear example of a genetically influenced behavior associated with a significant public health problem.

Molecular epidemiology involves collection of biospecimens to identify genes and molecular events that may link exposure to disease. Such studies require large trials and biospecimen collections, which has led to development of the Environment and Genetics in Lung Cancer Etiology, or EAGLE, study. This is a large case-control study with extensive biospecimen collection and deeper epidemiologic information than is usually collected in cohort studies. EAGLE data have supported an analysis that found an association between consumption of fresh red and processed meat and lung cancer risk. EAGLE also supports integrative epidemiology, in which behavioral data are incorporated with molecular epidemiologic data; this work will aid understanding of smoking behaviors by collecting information on nicotine dependence, depression, anxiety, and other factors associated with smoking. Information on treatment, survival, prognosis, and clinical factors also is collected.

Despite information about adverse health effects, Americans continue to smoke. Genetic factors may influence smoking behavior. A smoking Genome-Wide Association Study (GWAS) involving nearly 5,000 subjects suggests that genetic differences in the nicotinic receptor may be related to smoking intensity (cigarettes per day). Genes in the dopamine pathway, which mediate reward from smoking, also may influence smoking behavior. A GWAS involving 13,000 lung cancer cases and 19,000 controls is under way to identify genes that may interact with smoking to affect lung cancer risk. Preliminary results suggest that a locus on chromosome 15 that encodes the nicotinic receptor is strongly associated with lung

cancer after adjustment for smoking, as is a locus encoding a telomerase on chromosome 5 and another site located within the HLA region.

The sustained efforts of the intramural program have led to these breakthroughs, and its support of large studies and consortia has been crucial. EAGLE has provided sufficient numbers of cases and the opportunity to integrate molecular and behavioral data. Two other consortia that will be instrumental are GENEVA, which provides support for GWAS, and the International Lung Cancer Consortium, which represents more than 40 lung cancer studies with more than 40,000 cases. Priorities for further research include the genomics of outcome (e.g., the influence of genetics in treatment efficacy and survival) and studies of key population subgroups, such as African Americans (who have higher lung cancer incidence despite lower smoking rates) and nonsmokers who develop lung cancer.

Dr. Dennis said that preclinical studies permit evaluation of new drugs and new drug combinations in relevant model systems; exploration of mechanisms of lung carcinogenesis; validation of genetic expression profiles that may be predictive or prognostic; analysis of the tumor microenvironment; and pharmacokinetic, pharmacodynamics, and toxicology studies. A variety of lung cancer model systems are available, including normal airway and lung cancer cell lines, and mouse xenograft and tobacco carcinogen-driven models. Models for never-smokers also exist; most are driven by mutations in the epidermal growth factor receptor (EGFR).

One preclinical lung cancer treatment study targets a signaling pathway that, when activated, promotes cancer cell survival, proliferation, and migration. Key components of this pathway—PI3 kinase, AKT, and mTOR—are activated by nicotinic receptors and tobacco carcinogens. Triciribine, which inhibits AKT, and rapamycin, which inhibits mTOR, were tested in a mouse tobacco-induced lung cancer model. Treatment with rapamycin after carcinogen exposure decreased tumor size by 50 percent. When rapamycin treatment began within 1 week after exposure, tumor size and multiplicity were reduced by 90 percent.

Another approach to preventing lung cancer in smokers involves manipulation of immune cells. After tobacco carcinogen exposure, numbers of FOXP3+ T regulatory cells increase only in lung tissue. These cells suppress cytotoxic T cell activity, creating a permissive environment for cancer growth. Rapamycin decreases numbers of carcinogen-induced FOXP3+ T regulatory cells before the tumor is established; after tumor growth occurs, rapamycin decreases tumor size by 50 percent but has no effect on T regulatory cells. However, if FOXP3+ cells are eliminated using genetic ablation or an antibody approach, 80 percent inhibition of oncogene-driven lung tumorigenesis is observed.

Lung cancer in never-smokers often is attributed to aberrantly activated EGFR. Never-smokers treated with EGFR inhibitors such as gefitinib and erlotinib develop resistance to these drugs. Four mechanisms of resistance have been identified, all of which are associated with maintenance of AKT activation; thus, inhibition of AKT could resensitize the tumor to EGFR inhibitors. Cells with mutated EGFR were treated with triciribine to inhibit AKT, along with EGFR inhibitors. When given in combination, gefitinib and triciribine synergistically inhibited cell survival and proliferation as well as activity of AKT and other downstream pathway substrates. Treatment with erlotinib and triciribine inhibited growth of xenografts in immune-deficient mice by 50 percent, although no effect was observed when each drug was used separately.

The intramural program supports development and use of preclinical cell and mouse models with relevance to many molecular subsets of lung cancer. These models aid in understanding lung cancer and in developing targeted therapeutics. The Program also minimizes barriers between preclinical and clinical lung cancer research; a lung cancer prevention trial with rapamycin and a lung cancer treatment trial of triciribine and erlatinib are currently undergoing approval.

Dr. Giaccone told members that a significant challenge to treating lung cancers is determining the correct treatment for each patient. The Clinical and Translational Program seeks to refine classification of lung cancers and thus permit better targeted treatment. To this end, studies on large retrospective case series are underway to identify molecular prognostic and predictive markers and genetic alterations that may represent therapeutic targets in lung cancer and thymomas. The Program also plans to conduct prospective molecular profiling of all patients seen at the NCI Medical Oncology Branch and clinical studies of targeted agents for molecularly defined patients.

Clinical specimens are collected, processed, and stored using a standardized procedure and the integrated database Labmatrix™. These specimens are presently being processed for comparative genomic hybridization (CGH) and mutation analysis of selected genes; analysis of micro RNAs expression and validation by *in situ* hybridization; and creation of primary cancer cell lines to aid in tumor classification. One project involves correlating expression profiles of specific micro RNAs with survival in 800 specimens from a large randomized study testing whether chemotherapy in an adjuvant setting improves survival for non-small cell lung carcinoma (NSCLC). Another study has used clustering analysis of CGH data to show that most SCLC segregate independently from other neuroendocrine tumors and also has identified another cluster of tumor types that are currently difficult to classify based on histological characteristics.

Thymoma is a rare tumor of the epithelial cells of the thymus, but is the most common cancer in the anterior superior mediastinum. The current histological classification is not highly informative regarding survival or tumor behavior and is poorly reproducible. CGH analysis has reclassified type A thymomas as the most differentiated; types B3 and C appear to be genetically similar, but show significant genomic imbalance and genetic alterations compared with type A. Clustering analysis will be used to develop a classification system for these tumors with improved predictive value. The Program also is organizing a workshop on thymic malignancies to discuss the biology of thymomas and how the current classification scheme can be improved. A Phase II study of a histone deacetylase inhibitor (belinostat) for thymoma also is underway; two major responses have been observed in patients who were refractory to several prior treatments.

Molecular profiling of individual patients to target treatment is in progress. In never-smokers who develop resistance to EGFR inhibitors and have wild type EGFR, drugs that block EGFR and other members of the EGFR family (HER2 and HER4) as well as heterodimerization among these molecules appear to provoke a response in some patients. The mechanisms of resistance to EGFR inhibitors appear to be multiple and molecular profiling of these tumors will be essential.

Extensive molecular profiling of lung and thymic malignancies may improve treatment decisions. Certain subtypes of lung cancer that may be less complicated than those found in smokers will be analyzed, such as lung cancers occurring in people who never smoked, women, patients younger than 40, familial and rare histological types of lung cancer and patients with lung cancer and HIV. Mutation analysis of molecules known to be implicated in lung cancer will be performed, as well as fluorescent *in situ* hybridization to identify relevant translocations and amplifications, genome-wide screening using CGH and Solexa sequencing, and analysis of circulating tumor cell DNA and micro-RNA.

There are emerging etiologic, clinical, and molecular data indicating that lung cancer is a family of related, but distinct diseases. Molecular profiling shows promise for distinguishing among patients and could help to focus clinical trials on subsets of patients. NCI could play a major role in identifying lung cancer subtypes and matching them to the appropriate treatment; accrual will be a challenge for these types of studies that focus only on a small percentage of the lung cancer patient population. Patient accrual and tissue availability also need to be better integrated with detailed patient characterization to fully explore the use of molecularly defined subgroups for prevention, screening, diagnosis, treatment, and followup.

Questions and Answers

Dr. Chabner acknowledged that multi-institutional trials will be needed to develop focused clinical trials to allow patients to be treated based on the molecular characteristics of their tumors. Dr. Lyerly added that NCI has unique capabilities for facilitating such trials. One barrier faced by academic medical centers is obtaining tumor samples after recurrence (or progress) on therapy. NCI's capability to acquire those tissues and coordinate fundamental studies of resistance mechanisms would be valuable to the field.

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, commented that the cure rate for lung cancer in the United States has increased only from 5 to 7 percent in the 1970s to 15 percent in 2009. A priority for lung cancer research should be developing a predictive risk model for lung cancer among smokers (50 percent of cases occur in former smokers) to identify those at extremely high risk of developing lung cancer and target those individuals for intensive screening, early detection, and chemoprevention efforts.

Dr. Coffey raised several concerns about concordance for lung cancer in monozygotic twins, given that less than 50 percent of identical twins develop the same cancers; one large study showed a concordance of 42 percent for prostate cancer. He asked how this would affect the ability to apply personalized approaches to this cancer. Dr. Caporaso answered that one twin study showed modest concordance, and he agreed that the environmental aspects of lung cancer will present challenges to developing risk models. He acknowledged that including genetic variants in risk models has not greatly increased their predictive ability. Dr. Coffey noted that not all heavy smokers develop lung cancer; similarly, only 85 percent of syngeneic identical twin mice used in smoking experiments develop lung cancer. He asked how expression of genes hypothesized to be involved with lung cancer development in these mice would affect lung cancer rates. Dr. Dennis responded that it was not possible to answer the question at this time. However, subunits of nicotinic receptors identified as relevant to lung cancer in the GWAS are being crossed into mice that do not express these subunits. The receptor subunits also will be crossed into a tobacco-susceptible strain, and the mice will be analyzed after treatment with a carcinogen.

Dr. Coffey asked if an immune-based approach to lung cancer treatment was being considered, for example suppressing CTLA4 cells with rapamycin, and whether any vaccine trials for lung cancer were underway. Dr. Dennis answered that approaches to eliminate T regulatory cells appear promising; the presence of T regulatory cells or FOXP3+ cells may be associated with poor prognosis. Another complication is that T regulatory cells appear to inhibit progression of chronic obstructive pulmonary disease (COPD), which is often found in heavy smokers. Suppressing T regulatory cells to treat or prevent lung cancer could worsen COPD and increase inflammation.

Dr. Daniel D. Von Hoff, Physician in Chief and Senior Investigator, Translational Genomics Research Institute, and Clinical Professor of Medicine, University of Arizona, suggested developing a clearinghouse for providing access to different patient subtypes and information measured in a clinical laboratory improvement amendments (CLIA)-certified environment. In addition, Dr. Von Hoff described his own experience with obtaining biopsies after treatment; it may be more ethical to perform a second biopsy to determine whether the treatment has affected the intended target rather than protecting patients from a second biopsy.

Mr. Koch asked if studies of lung cancer metastasis to brain were being considered. Dr. Giaccone answered that mouse models are being used to understand the molecular profiles of lung cancers that metastasize to brain and also to identify genes that regulate the metastatic pathway; such genes may be drug targets for both treating and preventing brain metastasis. Brain metastasis occurs in more than 50 percent of SCLC patients who survive beyond 1 year; it occurs in less than 20 percent of NSCLC patients at diagnosis but increases to 30 or 40 percent with prolonged survival.

Dr. Jennifer A. Pietenpol, Director, Vanderbilt-Ingram Cancer Center, and B.F. Byrd, Jr. Professor of Oncology, Vanderbilt University Medical Center, explained that her institution plans to offer tools to detect 100 mutations by the end of the year and use an electronic medical record system to record a patient's mutation status within 1 to 2 weeks of their visit to align mutation status with treatment. The charge for this will be between $2,000 and $4,000, the majority of which is not covered by insurance. Dr. Niederhuber agreed that NCI has the resources to help provide these types of services to patients, but cannot bring all the patients to the trial. Interaction among institutions, academic centers, and community physicians—85 percent of patients are treated in the community—is crucial.

VII. NCI'S ROADMAP TO PERSONALIZED MEDICINE DR. JAMES H. DOROSHOW

Dr. James H. Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), provided an overview to NCI's roadmap to personalized cancer treatment. Dr. Doroshow said that, with the majority of new therapeutic targets coming from the academic community, the NCI is considering how its resources can best enhance personalized medicine in the community. The Institute's timeline for developing therapeutics encompasses hypothesis generation, clinical candidate development, and commercialization of agents. To expedite the development of personalized cancer treatment through Phases I through III clinical trials, the NCI is working to improve the specificity of treatment while reducing the high rate of failure and cost during transitions between trial phases.

Dr. Doroshow described contributions of Clinical Trials Working Group (CTWG) and Translational Research Working Group (TRWG) implementation to personalized therapeutics through several programs that provided timely prioritization and dedicated resources for biomarker validation, accelerated research initiatives, and supported the coordination of hypothesis-driven biomarker studies across the translational continuum. These programs include: the Biomarker, Imaging, and QOL Studies Funding Program (BIOQSFP); Special Translational Research Acceleration Program (STRAP); and Grand Opportunity grant vehicle to coordinate clinical and translational research across the NCI. 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 refinement of the NCI Experimental Therapeutics (NExT) drug development pipeline, particularly with the reorganization of the Rapid Access to Intervention Development (RAID) program, elimination of one-third of the pipeline and recent reprioritization of activities around the development of new cancer drugs and biologics, and the NExT Center's relationships with caBIG and the intramural and extramural communities.

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. The NCI is addressing this "pharmacogenomics divide," but the process is complicated. Dr. Doroshow illustrated this by an example of tamoxifen pharmacology and the recent recognition that tamoxifen metabolites can exhibit differences in 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; however, intellectual property rights are not possible for a 30-year-old metabolite although it is a new "drug." Hence the NCI is producing a clinical grade drug to begin the process leading to a Phase I study of endoxifen.

To handle similar issues on a larger scale, the NCI is committed to developing a Chemical Biology Consortium (CBC) that integrates chemists, biologists, and molecular oncologists from academic and pharmaceutical organizations, along with synthetic chemistry support, to focus on "undruggable" targets 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 described work on the Tdp1 protein as a demonstration of the effectiveness of this collaborative approach. He said 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 4 to 6 years.

Questions and Answers

Mr. Koch asked whether the NCI has a program to license its patents to biotechnology and large pharmaceutical companies and whether specific licensees with compatible capabilities to exploit inventions are sought. Dr. Doroshow replied affirmatively, and Dr. Barker explained that the NCI has a big patent portfolio, including the intellectual property, and the patent program emphasizes non-exclusive licenses. She noted that the NCI's intramural investigators also collaborate in the process with the NCI technology transfer group. Dr. Niederhuber added that the NCI has hosted and shown the Institute's resources to major pharmaceutical companies to establish relationships at the highest level of large industry, which in time disseminate to smaller companies. This effort helps leaders in the private sector recognize that the NCI envisions strong partnerships between the academic community and the private sector. Mr. Ingram agreed with Dr. Niederhuber on the importance of collaboration among the NCI, academic health centers, comprehensive cancer centers, and the private sector to ultimately benefit patients. Mr. Koch requested illustrative examples of licensing from the NCI that has saved lives, and Dr. Barker referred to taxol, human papillomavirus (HPV), and AIDS drugs as illustrative of the process. She suggested that the drug development roadmap may be useful in winnowing down the number of targets that forthcoming The Cancer Genome Atlas (TCGA) ovarian data are expected to yield.

VIII. CANCER CENTERS SUBCOMMITTEE REPORT AND FUTURE AGENDA ITEMS DR. CAROLYN D. RUNOWICZ

Cancer Centers Subcommittee Report. Dr. Lyerly, Chair of the NCAB Cancer Centers Subcommittee, informed members that there was robust discussion at the meeting regarding two areas: 1) the proposed change in the modification of the NCI Cancer Center Support Grant (CCSG) Guidelines; and 2) the role of the Cancer Centers in community involvement and their impact on community health and access to care.

The Subcommittee discussed the fact that the Cancer Center programs are very successful, but their success must be balanced with new opportunities, especially with the role of Clinical Translational Science Awards (CTSAs) and their impact on the local environment, and how they interact with the Cancer Center's leadership, and promote collaborative research.

The CCSG Guidelines should enable industry collaborations that have potential for rapid manufacture of products for humans that target new molecular entities. The Guidelines cannot prescribe specific details and opportunities, but they can issue directives regarding which principles and policies should be addressed. The Subcommittee, in helping to revise the Guidelines, will be engaged more actively to provide support and create opportunities; for example, ensuring that individuals serving as part of a research team are not penalized for not being the first author in related publications. Dr. Runowicz referred members to the 10 June Subcommittee meeting minutes for the timeline for revising the guidelines.

Motion. A motion was made to approve the minutes of the 10 June 2009, NCAB Cancer Centers Subcommittee meeting. The Board unanimously approved the minutes.

Future Agenda Items. Dr. Runowicz noted that, based on discussions at the February meeting, a Global Cancer Research Subcommittee will be formed, and she invited any NCAB members to express

their interest in serving on this committee to Dr. Gray. Members also were asked to provide their input for future agenda items and on the modified meeting format that includes questions for the NCAB at the end of presentations.

IX. APPLICABILITY OF MOUSE MODELS IN TRANSLATIONAL RESEARCH AND PERSONALIZED MEDICINE DRS. DINAH SINGER, TERRY ANNE VAN DYKE, AND CHERYL MARKS

Dr. Dinah Singer, Director, Division of Cancer Biology (DCB), informed members that the NCI made a commitment a decade ago to develop genetically modified or other mouse models that could faithfully recapitulate the human disease, and that today's presentations illustrate how mouse models can be integrated into the entire spectrum of cancer research, including prevention, diagnosis, drug development, and therapy. Dr. Singer introduced the speakers: Drs. Terry Anne Van Dyke, Director, Mouse Cancer Genetics Program, NCI Center for Cancer Research (CCR); and Cheryl Marks, Associate Director, Division of Cancer Biology (DCB).

Dr. Van Dyke told members that more than 100 cell types in the mammalian body are susceptible to cancer, each with multiple molecular etiologies. Current preclinical systems identify toxicities well but are less useful in identifying efficacies; only 5 percent of drugs are approved, and often these do not work as they did in the preclinical systems. During the past 20 years, genetically engineered models (GEMs) have been used to code the biology of cancer, some of which now are ready for preclinical work. The goal is to use better models to identify drugs for clinical trials. Knowledge gained from clinical trials can be used to engineer and initiate cancer in mouse models with specific genetic events targeted. The progression of the disease can be documented, and samples taken throughout the process can aid research on prevention and disease etiology.

As an example, in non-small cell lung cancer, the EGFR is mutated in approximately 10 percent of the cases (typically in nonsmokers), and approximately 75 percent of these cases respond to an EGFR blockade. Additionally, in the same molecular pathway, Kras is mutant in a mutually exclusive population of cancers. If the same therapy is used on all these patients, those with the Kras mutation do not respond to the EGFR blockade; those patients fared better on chemotherapy alone. A better method to identify which patients will respond to a given treatment is needed, because current methods used to develop targeted therapies search throughout multiple complex pathways and nodes for an appropriate molecular target. From the initiation of cancer, the diseased cell is engaged in "crosstalk" with the entire tissue, essentially developing a new organ. Therefore, at least four points must be considered in cancer drug development: tissue specificity, pathway specificity, results of drug therapy on feedback loops (ras treated by EGFR), and resistance. Specific models are able to guide clinical research in cases in which examination of all of the previous factors in human patients would be almost impossible. For example, the mutation in the EGFR blockade resistant population was created in a mouse model, and a study found that two blockades (one an irreversible inhibitor) together worked well in shrinking tumors. A clinical trial based upon this finding has been designed at the Dana Farber Cancer Institute. For the ras patients who do not respond to these therapies, a similar model with a resistant mutation built in can be treated with an inhibitor of either one of the major pathways or another pathway regulated by the ras protein. The combination of therapies proved dramatically effective, and should lead to clinical trials in ras mutant patients. In each of the types of cancers for which models are available, multiple GEMs now exist.

Dr. Marks informed members that mouse cancer models are defined as: 1) normal inbred laboratory mice and their crosses; 2) mice whose genomes are engineered to initiate spontaneous cancer development; and 3) mice that are exposed to carcinogens to generate spontaneous tumors. Mice are used because of their similarities to humans with respect to genome, immune function, natural history of cancer progression, and heterogeneity of population genetics.

Mouse models can contribute to understanding human cancer genetics by exposing factors that may increase the risk of susceptibility to cancer. In a study that examined the interactions of dietary fat, obesity, and metastasis of mammary cancer in a mouse model that was a cross between a breast cancer model and a diet-induced obesity model, a key finding is the ability to locate the regions in the mouse genome that confer susceptibility to diet-induced obesity and its effect on breast cancer. In an NCI-funded project, the International Complex Trait Consortium is generating and genotyping approximately 700 strains of a new mouse genetic resources from eight diverse founder lines. When completed, this resource will display more genetic heterogeneity than what is observed in human populations, and will be used to find genetic and environmental determinants of cancer.

Dr. Marks said that mouse models can contribute to drug development through their use as a biological context to identify new targets, validate the role of those targets in disease biology, determine whether the targets are efficacious, and expose the genetics of response and toxicity. The very early stages of diseases can be seen in mouse cancer models, and often they are used for both prevention mode and therapy. Observations of disease in the models can be used in an iterative cross-species approach with humans to design clinical trials. Also, because the entire progression of the disease can be monitored, various interventions can be attempted to determine when a prevention agent can be used, and what biomarkers there are to predict efficacy. Another component of importance is drug safety and toxicity. The models are a tractable system that can be used for mechanistic studies to predict occurrence of secondary malignancies that may occur years after treatment of pediatric malignancies. Additionally, the pathology of genetically engineered mouse models that are missing genes may instruct researchers as to which diseases or which organ systems are likely to be affected by the use of targeted drugs.

Questions and Answers

Mr. Koch asked if NCI engaged in the development of more human-like mice. Dr. Van Dyke replied that strong research in both the intramural and extramural programs is ongoing on humanized gene and humanized organ models of mice. Mr. Koch wondered whether therapies that failed in mice always were abandoned despite the possibility of proving effective in humans. Dr. Van Dyke said that most often, therapies that fail in mice are abandoned, but that humanized mouse models hold promise. Dr. Marks added that pharmaceutical companies are attempting to retest some of the failed drugs with the new mouse cancer models, because results from agent testing in mouse cancer models and human transplantation models are helpful in understanding why an agent did not give the expected clinical results.

The relevance of mouse models for studying drug efficacy, side effects, and resistance to EGFR inhibitors was discussed. Dr. Chabner questioned the relevance of mouse models for analysis of organ toxicities associated with these drugs, noting that most EGFR inhibitors are relatively non-toxic in humans. Dr. Van Dyke explained that the EGFR inhibitor side effects observed in mice differ based on strain background; this system could be used to identify genes influencing susceptibility to toxicities and predict individual susceptibility to specific side effects. Dr. Chabner contended that much information about EGFR inhibitors had been gleaned from studies in cell culture systems, particularly drug resistance for targeted drugs, and thus cell culture might be better than mice for such analyses. Dr. Marks agreed that cell culture systems had been informative but noted that information from genetically engineered mouse models, in conjunction with data from cell culture systems, would be most effective for generating data necessary for improving clinical practice.

Dr. Hong encouraged the promotion of integrated tumor research in mouse models, such as by integrating mouse-related research and translational research through the Mouse Consortium Special Program of Research Excellence (SPORE) group. Dr. Marks agreed.

Dr. Von Hoff recommended that the GEM mice discussed should be made available to researchers and noted that it would be useful if the mice were staged with ultrasound to ensure that the tumors are of

equal size. Dr. Van Dyke agreed and noted the work of the CCR's Center for Advanced Preclinical Research in this area. Dr. Marks added that an NCI mouse repository in Frederick, Maryland has strains available free of charge to investigators.

Dr. Kaur asked about what is the appropriate proportional relationship among research using cell cultures, humanized model systems, and basic mouse models to prioritize the dollars spent on technology. Dr. Van Dyke said that an integrated approach was necessary and the best use of resources.

X. SCIENTIFIC UPDATE ON THE CENTERS FOR POPULATION HEALTH AND HEALTH DISPARITIES DRS. SHOBHA SRINIVASAN, ELECTRA PASKETT, SARAH GEHLERT, AND TIMOTHY REBBECK

Dr. Shobha Srinivasan, NCI Centers for Population Health and Health Disparities (CPHHD), informed members that the CPHHD has existed for 5 years; was funded by the National Institute of Environmental Health Sciences, NCI, the National Institute on Aging, and the Office of Behavioral and Social Science Research; and currently collaborates with the National Heart, Lung and Blood Institute (NHLBI). The Cells to Society Program is a trans-NIH scientific effort that examines basic to population sciences to address inequities in cervical, breast, and prostate cancer. The pathways in these cancers are very similar, and understanding them would aid in the understanding of whether the pathways enhance or inhibit tumorigenesis in both mice and humans, which has impact for both prevention and intervention. The three centers represented in the following presentations are based within the Cancer Centers and benefit from the science of both Cancer Centers and CPHHD. Dr. Srinivasan introduced the speakers: Drs. Electra Paskett, Ohio State University; Sarah Gehlert, Center for Interdisciplinary Health Disparities Research (CIHDR), University of Chicago; and Timothy Rebbeck, Abramson Cancer Center, University of Pennsylvania.

Overview. Dr. Paskett stated that CPHHD's mission was to: integrate basic population and clinical sciences, develop innovative transdisciplinary methods, create linkages with the community, and translate research to change policy and practice. Research teams initially functioned as multi-disciplinary, with members having separate bodies of knowledge and distinct vocabularies, or interdisciplinary, with a shared body of knowledge and vocabulary, but CPHHD now uses a transdisciplinary model, which involves a shared language, pooled bodies of knowledge and theory, and new jointly developed research methods. Another important element of the CPHHD is the transdisciplinary research framework, which includes community-based participatory research that encompasses basic science (biomarkers or animal model studies), preclinical and clinical studies, and the impact on the patient and community.

Multi-Level Factors and Cervical Cancer Risk in Ohio Appalachia. Dr. Paskett told members that the Community Awareness Resources and Education (CARE) Center at Ohio State University focuses on cervical cancer in an exclusively rural population in Ohio Appalachia to determine why cervical cancer incidence and mortality rates among white women in Ohio Appalachia are high (2002 data). CARE also has two intervention projects attempting to reduce this mortality. CARE examined three major areas: PAP test screening, smoking, and HPV infection. Findings revealed that although 79 percent of the women in the study were at high risk of developing cervical cancer, only 69 percent had been screened. Following an intervention that used lay health advisors to attempt to increase PAP screening in the community, 73 percent of the women in the intervention group had received a PAP test versus 54 percent of the women in the control group. Further investigations on the prevalence of the TGF-beta *6A susceptibility allele in this population is underway. Tobacco use in Appalachia is higher than in the U.S. population (28% vs. 21%). The study found that 69 percent of the women with abnormal PAP test results smoked, smokers had fewer social contacts, and depression was more common among smokers. Following a second intervention using a lay health advisor to improve smoking cessation rates, the percentage differences in smoking cessation at 3 months and 6 months between the intervention and control groups were a statistically significant 16 and 9 percent, respectively. CARE's third study estimated the prevalence of HPV in Appalachian women.

Compared to the U.S. population, there is twofold elevation in the rates of any HPV type, and twofold elevation in high risk types in this population. HPV Types 16 and 18, those related to cervical cancer, show more than a fivefold prevalence in the Appalachian population. The uptake of the HPV vaccine in the United States is approximately 25 percent versus 10 percent in the Appalachian population. The vaccine's acceptability is low in Appalachia based on local knowledge, attitudes, and beliefs. Additionally, access is low due to the high cost and low supply of the vaccine. Finally, response to the vaccine may be low in women with compromised immune function. Dr. Paskett said that CARE-II consists of four projects: examination of TGF-beta receptor polymorphisms in basic cervical cancer in West Virginia; study of the effect of social networks on smokers and their potential for use in smoking cessation; study of the immune response to the HPV vaccine; and a multi-level intervention to increase uptake of the HPV vaccine.

Breast Cancer and Social Interactions: Identifying Multiple Environments That Regulate Gene Expression. Dr. Gehlert described research on how factors in women's social environments contribute to the African American and white disparity in breast cancer mortality in the United States. She observed that white women are more likely to develop breast cancer than African American women, but African American women are 37 percent more likely to die from breast cancer.

Dr. Gehlert told members that CIHDR's work involves two animal models as well as work at the community level examining social circumstances and other factors. One animal study showed that isolated female rats developed a mammary tumor burden much higher than rats left in their social group; the corticosterone levels in the isolated rats remained higher after a stressor than did the grouped animals. This study was replicated in SV40-tagged mice, and it was found that glucocorticoid receptors increased as tumors became more invasive, which implies that the mice are susceptible to GR-mediated cell growth. Isolation led to upregulated fatty acid synthesis and glycolytic pathway mammary gland gene expression, which contribute to breast cancer growth, suggesting potential targets for intervention. Endocrine stress response should be considered in understanding the biology of health disparities; the hormone response is a conduit from social environmental stressors to gene expression. The CIHDR's work in humans examined aggressiveness of tumors, and social isolation and its psychological sequelae, which are felt loneliness, acquired vigilance, and neuroendocrine response. The team's investigations in rats showed that they became vigilant (e.g., constantly attuned to threats) when isolated, and remained so even when returned to social groupings. Informed by this work, the group enrolled African American women from three hospitals that serve uninsured, Medicaid, and privately insured patients in a study, and collected tissue when their tumors were excised. The women were interviewed over 1.5 years about a number of issues, including psychosocial functioning, social networks, health behaviors, and perceived discrimination, and dirunal salivary cortisol was collected at regular intervals. Data on crimes in the quarter mile around each of the women's houses were collected, as were data on the condition of housing, both of which affect acquired vigilance. The areas around the women's homes were measured for opportunities for and impediments to social interaction. A cluster analysis showed that 67 percent of the women showed endocrine burnout; cortisol rhythms are affected by neighborhood factors and social responses, and this must be considered in designing interventions. The CIHDR learned that biological factors with clinical implications can be predicted from neighborhood factors, which can be targeted with interventions. From the neighborhood-level degraded infrastructure, unsafe housing, and crime, there is a positive pathway through sexual assault to isolation, depression and loneliness, and anomie, and a positive pathway to cortisol response; in the animal model, glucocorticoid receptors in the cancers and upregulation of metabolic and inflammatory genes have been identified. In the women, 38 percent had triple negative tumors, primarily in the endocrine burnout group. There are significantly more of those women in the under 50 age group; additionally it was found that the number of sexual assaults experienced was associated with estrogen receptor negative status.

Dr. Gehlert said that in the second phase of the study, the CIHDR is testing a neighborhood support level coordinator intervention, and building on the molecular pathways tested earlier that might

provide targets for breast cancer prevention, such as fatty acid synthesis. There were changes in fat metabolism based on social factors detected that may lead to changes in fat distribution and, therefore, increased breast cancer as well as metabolic syndrome susceptibility. The CIHDR is testing this model on rural, impoverished white and African American women in the Missouri Boot Hill, and will follow food intake and food insufficiency, BMI, and other measures. Because all the women are of low socioeconomic status, this research provides an opportunity to distinguish the roles of race, socioeconomic status, and geography in health disparities.

Why Do Men of African Descent Have Unfavorable Prostate Cancer Outcomes? A Multi-Level Molecular Epidemiology Approach. Dr. Rebbeck presented research on the unfavorable prostate cancer outcomes for African American men in comparison to other groups. The disparity between African American and European American men for prostate cancer is the highest in terms of mortality for any of the major cancers. During the earlier CPHHD funding period, the Center used a model addressing the concepts of genetic susceptibility, biomarkers, early lesions, cancer, and cancer outcomes. This work is an attempt to understand the relationship between genetic susceptibility, individual exposures, and the neighborhood in the community context. The Center works with the National Black Leadership Initiative on Cancer to develop, conduct, and disseminate research.

Dr. Rebbeck informed members that much is known about some of the inherited genetic susceptibilities that have been identified. *RNASEL* and *MSR1* are two genes that appear to confer increased prostate cancer susceptibility when mutated in the germ line, and both are involved in immune function, inflammation, and the development of reactive oxygen species. Genotype effects on prostate cancer outcomes depend on context. The pattern of a gene that confers susceptibility in prostate cancer having its most significant effect on prostate-specific antigen (PSA) failure and poor outcomes in dysfunctional neighborhoods is seen with many genes. Another part of the Center's work involves determining what types of treatment in what contexts improve outcomes. Surveillance, Epidemiology and End Results (SEER) Medicare data on men older than 65, treated or untreated for prostate cancer, in both European American and African American populations were analyzed. The relative risk of death for all groups is higher in men who are untreated; the men who are treated have lower mortality, but this effect is much higher in the African American community. These data show that elderly men benefit from active treatment as compared to surveillance, and African American men appear to receive less appropriate treatment than European American men. Neighborhood-level data show that prostate cancer mortality also is affected by residential segregation. Men who live in unsegregated neighborhoods, whether they are African American or European American, have very similar outcomes, without differences in mortality; men who live in highly segregated environments have very disparate experiences in terms of treatment outcome and mortality. A third study at the University of Pennsylvania found that among men recently diagnosed with prostate cancer, African Americans fared better than European Americans in terms of emotional and physical wellbeing. Subsequent research has indicated that this might be explained by the quality of life that an individual is leading at the time of the cancer diagnosis. For men who have many stressors, the prostate cancer diagnosis might not be the most salient, and this situation may be more likely in the African American than the European American community. Another finding is that survivorship programs need to incorporate the cultural values of African American men, who have a greater orientation toward religion than European American men, in order to be successful. Dr. Rebbeck said that CPHHD2 will examine context-specific biomarker prediction, context-specific screening and treatment, and an African American-specific survivorship program specifically considering cultural and ambient quality of life issues. The approach will be to study levels of disease from early screening through cancer diagnosis, progression, and clinical outcomes and to develop and implement interventions based on neighborhood- and individual-level factors including biology and genetics.

Future Challenges for the Centers for Population Health and Health Disparities. Dr. Rebbeck informed members that common research themes among the CPHHDs include: genetic susceptibility and the regulation of gene expression; cumulative physiological dysregulation; biological effects of a

threatening social environment; and contextual effects of individual- and area-level factors. Additionally, a new transdisciplinary paradigm has been developed at the CPHHDs, which includes new research methods and tools; CER integrating biology, behavior, neighborhood, environment, and health care; and training, dissemination, and community involvement. However, the CPHHDs face challenges conducting this transdisciplinary research, including the successful enhancement of the integration of disciplines and the maturation of the emerging scientific themes mentioned above. Additionally, the CPHHDs must develop and test comparative effectiveness interventions by: exploiting the synergies of population health, biology, and personalized medicine; creating targeted screening and prevention strategies; using novel therapies and novel applications of existing therapies; optimizing health care use; and creating an impact on policy.

Questions and Answers

Dr. Champion asked if the lay health advisors mentioned by Dr. Paskett were professionals or community trained and whether followup was conducted on the women with positive PAP smears. Dr. Paskett responded that they were members of the same Appalachian communities as the women they were visiting, and were employed by CARE. She added that the lay health advisors were involved in getting the women into followup care, as were the Appalachian Community Cancer Network and the Ohio Breast and Cervical Cancer Program.

Dr. Meneses noted the importance of leveraging complex conceptual modeling in the next phase of CPHHD and wondered how long the investigators would be engaged with the patients and underserved groups in their studies. Dr. Rebbeck explained that it was a long-term process and could not be accomplished in a 5-year grant period. Dr. Paskett added that trust is built over many years, and that CARE keeps the Appalachian community coalitions engaged by helping them write grants for research funds that directly benefit the communities.

Dr. Kaur commented that the presentations illustrate that disparities are not based only on differences in access to care, but biological, social, and cultural issues involved in both cancer etiology and cancer treatment. She encouraged collaborations with the NHLBI to address comorbidities and determine interventional methods that are effective for diabetic control and heart disease control as well as the risks and treatment of cancer. Dr. Rebbeck agreed that the integration of medical care is critical.

Dr. Coffey recommended that endocrine factors be included in these studies and that these be examined to determine how inflammation and the cytokines are involved in prostate cancer; he also suggested that Asian groups should be studied in addition to Caucasian and African American populations, as should the impact of housing changes on human stress. Dr. Gehlert agreed that lack of safe and affordable housing is the most significant stressor found in her studies.

Ms. Mary Vaughn Lester, Board of Directors, University of California, San Francisco Foundation, asked the presenters if their studies were age specific or random. Dr. Paskett said that the studies examine a wide range of ages. The HPV virus is more prominent in younger patients, but the results in her presentation were from women 18 years and older. Dr. Gehlert indicated that she sees more triple negative and estrogen receptor negative tumors in African American women under 50.

Mr. Koch asked if prostate cancer outcome data on different racial groups in similar economic circumstances were collected. Dr. Rebbeck confirmed this and explained that self-identified race is a poor marker of many key events and outcomes; his study used genomically determined ancestry information and socioeconomic, behavioral, and quality-of-life metrics. Mr. Koch noted that an extreme example of isolation and stress is the prison population, and asked if the presenters had considered studying this population. Dr. Gehlert replied that they have not because of human subject institutional review board (IRB) issues, but did study rural women in Nigeria who had to leave their families for the city for economic reasons as an example of a severely isolated group.

XI. CLOSED SESSIONcDR. CAROLYN D. RUNOWICZ

This portion of the meeting was closed to the public in accordance with the provisions set forth in Sections 552b(c)(4), 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.

The *en bloc* vote for concurrence with IRG recommendation was affirmed by all serving Board members present. During the closed session of the meeting, a total of 2,445 applications were reviewed requesting support of $ 698,993,325.

XII. ADJOURNMENTcDR. 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 150th regular meeting of the NCAB was adjourned at 5:00 p.m. on Thursday, 11 June 2009.

_____ _____

Date Carolyn D. Runowicz, M.D., Chair

_____ _____

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