DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
152ND NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
December 1–2, 2009

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

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
Summary of Meeting
December 1–2, 2009

The National Cancer Advisory Board (NCAB) convened for its 152nd regular meeting on 1 December 2009, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, 1 December 2009, from 8:30 a.m. to 3:30 p.m., and Wednesday, 2 December 2009, from 8:30 a.m. until adjournment at 11:36 a.m., and closed to the public on Tuesday, 1 December 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
Dr. Bruce A. Chabner (absent)
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 (absent)
Dr. Diana M. Lopez
Dr. H. Kim Lyerly
Dr. Karen M. Meneses
Dr. Jennifer A. Pietenpol
Dr. Daniel Von Hoff (absent)

President's Cancer Panel
Dr. LaSalle D. Leffall, Jr. (Chairperson)
Dr. Margaret L. Kripke (absent)

Alternate *Ex Officio* NCAB Members
Dr. Michael A. Babich, CPSC
Dr. Patricia Bray, OSHA/DOL (absent)
Dr. Steven Kleeberger, NIEHS
Dr. Michael Kelley, VA
Dr. Richard Pazdur, FDA (absent)
Dr. John F. Potter, DOD
Dr. R. Julian Preston, EPA (absent)
Dr. Michael Stebbins, OSTP
Dr. Marie Sweeney, 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
Mr. Jim Dickens, Acting Director for Management and Executive Officer
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
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
Mr. Adam Clarke, Lance Armstrong Foundation
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. 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

TUESDAY, DECEMBER 1, 2009

WEDNESDAY, DECEMBER 2, 2009

TUESDAY, DECEMBER 1, 2009

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF 15–16 SEPTEMBER 2009 MINUTES—DR. CAROLYN D. RUNOWICZ

Dr. Runowicz called to order the 152nd 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 recognized the accomplishments of and recent awards received by several Board members, including: Drs. 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, who is the keynote speaker at the American Association for Cancer Research's (AACR) Conference on Frontiers in Cancer Prevention Research; Jennifer A. Pietenpol, Director, Vanderbilt-Ingram Cancer Center, B.F. Byrd, Jr. Professor of Oncology, Professor of Biochemistry, Vanderbilt University Medical Center, who was named one of 15 new members of Johns Hopkins University's Society of Scholars; and Richard Pazdur, Division Director, Division of Oncology Drugs, U.S. Food and Drug Administration (FDA), who was named a 2009 Alumnus of the Year by the Stritch School of Medicine at Loyola University.

Motion. A motion was made to approve the minutes of the 15–16 September 2009 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 2011.

III. NCI DIRECTOR'S REPORT—DR. JOHN NIEDERHUBER

Dr. John Niederhuber, Director, welcomed members and provided information about NCI's fiscal year (FY) 2009 and 2010 budgets and the American Recovery and Reinvestment Act (ARRA) investments supporting cancer science.

Budget. Dr. Niederhuber reminded members that the FY 2009 appropriation was $4.96 B, which is 2.9 percent higher than the FY 2008 operating budget of $4.38 B. NCI funds from the FY 2009 ARRA totaled $1.26 B. NCI's Budget Office closed the accounting books for FY 2009 with a balance of $4,432, representing a lapse rate of 0.00008 percent. In FY 2009, research project grants (RPGs) were funded at the 16th percentile plus extensive exceptions, for an overall 20 percent success rate. New investigator grants (R01s) were funded at the 22nd percentile plus an extended payline and exceptions, for a total of 183 awards. In FY 2009, the NCI funded 1,235 competing RPGs in addition to 543 RPGs supported through the ARRA. The NCI also added two new Cancer Centers: the Medical University of South Carolina and Emory University.

Dr. Niederhuber reminded members that the NCI continues to operate under a Continuing Resolution (CR) for FY 2010 until mid December. The FY 2010 appropriations bill has passed the House but awaits passage by the Senate. The House bill allocates $5.15 B and Senate bill $5.04 B to the NCI, providing 3.7 and 1.7 percent increases, respectively, from the FY 2009 level. The NCI currently is using the Senate's lower number for conservative planning purposes. The FY 2010 NCI budget recognizes

increases in mandatory expenses, including the cost of living, rent and utilities, small business set-aside, and NIH-wide assessments. The 2010 payline is estimated at the 16th percentile, and NCI leadership is striving to ensure that the success rate does not fall below 20 percent.

ARRA. The total obligated ARRA investments for the NCI in FY 2009 totaled $845 M. The Institute had obligated or committed all available ARRA funds by the end of the fiscal year. The existing balance of $400 M will be used to cover FY 2009 ARRA commitments and a limited number of FY 2010 NCI projects; these include program-specific administrative supplements as well as research and development contracts for the academic community.

Dr. Niederhuber said that the NCI has used careful and thoughtful planning to make investments that otherwise would have taken years to begin as well as to generate interest in science among Congressional legislators. These investments facilitate cancer research through an interactive platform of genomic and biologic studies, along with careful collection and analyses of high-quality tissue samples, through the NCI Experimental Therapeutics (NExT) pipeline, The Cancer Genome Atlas (TCGA) project, cancer Human Biobank (caHUB), and cancer Biomedical Informatics Grid (caBIG®). These support the study of high-risk and other tumors through characterization centers that help to translate data for use by practicing oncologists and thus improve diagnostics, disease management, and patient care. Dr. Niederhuber said that the vision is to make it possible for every cancer patient to participate in a national clinical trial; ideally at the time of diagnosis, each patient would be consented for their electronic health record, patient data, and tumor genomic characterization for ongoing and future studies. The data would include the chemical evaluation and tissue characterization, genomic changes, and relevant patient information about biomarkers, circulating tumor cells, imaging, targeted and combination therapies, and infectious agents. Dr. Niederhuber reminded members that the NCI therapeutics platform supports this focus on personalized medicine by connecting researchers from the private sector and academic research laboratories and by using caBIG® to connect and protect patient and clinical data.

Dr. Niederhuber concluded with the five themes that Dr. Francis Collins, Director, NIH, wishes for the NIH to focus on and noted the NCI's long commitment to these areas: 1) high-throughput technologies applied to fundamental biology; 2) translation; 3) use of science to inform health care reform; 4) global health; and 5) empowerment of the biomedical research community. Dr. Niederhuber concluded with ideas on moving the NCI forward, including an emphasis on seeing science impact patients and reducing the cost of health care.

Questions and Answers

Ms. Kathryn Giusti, CEO and Founder, Multiple Myeloma Research Foundation, Inc., asked Dr. Niederhuber what he would say to patient groups about what the ARRA has accomplished to advance patient care or patient issues in oncology. Dr. Niederhuber responded that the ARRA funds are supporting a number of programs that improve the ability to diagnose and manage cancer; the investments are based on making a difference in patients at some point in time. Ms. Giusti suggested that NCI's communication products, such as its project summary materials, might be refined to better convey the idea that ARRA investments are intended to have an impact on patients.

Ms. Giusti also queried about the NCI's role in engaging a seemingly reluctant industry in the personalized medicine effort to conduct the right trials and deliver the best therapeutics to individual patients. Dr. Niederhuber pointed out advances in knowledge about glioblastoma and ovarian cancers that have occurred, as well as the use of mathematical modeling in the functional space to understand how these observations play out in biology, such as in multiple cellular pathways. He said that pharmaceutical companies who visit the NCI acknowledge that this is a period of change in oncologic drug development and are beginning to recognize the resources of the NCI, including its role in early work at the transcriptional level; the NCI provides an enabling platform for interactions between the academic research

community and the private sector. Dr. James H. Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), added that the NCI sees a particular role for itself in supporting high-risk projects in areas of value, such as biomarker development.

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, reminded members about the experience working with molecular mammogram or molecular PSA biomarkers to illustrate that caution is needed to ensure that the correct surrogate markers are chosen. Dr. Niederhuber answered that current data are promising and likely will yield key patterns of gene expression and regulation, and key genes that are involved to determine the risk level. In the next few years, this information will be helpful during cancer screening to identify which cases require aggressive therapy.

Dr. Anthony Atala, Director, Wake Forest Institute for Regenerative Medicine, Professor and Chairman, Department of Urology, Wake Forest University School of Medicine, said that identifying every patient as a possible patient for a clinical trial or a cohort and capturing the appropriate data is an exciting notion, but he wondered about initiatives to standardize data collection. Dr. Niederhuber indicated that this is the purpose of caBIG®, which is focusing on the Cancer Centers as well as other data collectors.

Dr. Runowicz expressed appreciation for the update, particularly on NCI efforts in cancer therapeutics, and suggested that NCI's vision of cancer prevention could be shared at the February Board meeting. Dr. Niederhuber said that the ongoing work will contribute immensely to the understanding of prevention, which should be considered scientifically as managing the risk of developing cancer as a set of diseases, including through tailored screening. Dr. Victoria L. Champion, Associate Dean for Research, Mary Margaret Walther Distinguished Professor of Nursing, Center for Research & Scholarship, Indiana University School of Nursing, commented that additional issues to identifying risk include patient and care provider behaviors and activities. Dr. Niederhuber agreed on the importance of working at both individual and social levels.

IV. PRESIDENT'S CANCER PANEL—DR. LASALLE D. LEFFALL, JR.

Dr. LaSalle D. Leffall, Jr., Chair, President's Cancer Panel (PCP, the Panel) and Charles R. Drew Professor of Surgery, Howard University Hospital, thanked the NCAB and noted that the PCP consisted of himself and Dr. Margaret Kripke; a third panel member will be appointed by the White House. The mission of the PCP is to monitor the development and execution of the National Cancer Program and report directly to the President. The PCP should notify the President immediately of any delays or impediments to the National Cancer Program's progress.

The PCP's report on its 2008-2009 meeting series, Environmental Factors in Cancer, is nearly complete and is expected to be released in January of 2010. The 2009-2010 meeting series, America's Demographic and Cultural Transformation: Implications for the Cancer Enterprise, is underway, with meetings already held in Seattle, WA, and Los Angeles, CA. Additional meetings will be held in Wilmington, DE, and Miami, FL. The series will explore the implications for U.S. cancer trends as the proportion of ethnic subpopulations increases and whether the current cancer screening guidelines will continue to be appropriate in light of this increase. Additionally, the series will address: whether biologically based differences exist between ethnic groups in clinical presentation or response to cancer treatment; whether the clinical encounter differs across ethnic groups; and if patients from ethnic subpopulations differ from mainstream populations in their understanding, experience, and discussion of cancer.

At the Seattle meeting, participants noted that medically underserved populations are disproportionately minority, impoverished, and undereducated. It was also discussed that in the future

there will not be a single majority ethnic group. Fundamental societal changes must occur, because health disparities will persist as long as racism and disproportionate poverty continue. Participants at the Los Angeles meeting stated that variations in socioeconomic, cultural, and behavioral factors do not account for the entirety of racial and ethnic differences in cancer outcomes, and more molecular and genetic studies are needed. Additionally, research data based on non-Hispanic white populations may not be applicable to the current and projected populations within the United States. Meeting statements and further information on upcoming meetings can be found on PCP's Web Site (http://deainfo.nci.nih.gov/advisory/pcp/pcp.htm).

Questions and Answers

Ms. Giusti asked about the status of a Panel replacement for Mr. Lance Armstrong, and whether a celebrity member benefits the panel. Dr. Leffall responded that Mr. Armstrong was an outstanding member of the Panel, and his presence brought more participation to the meetings. Mr. Joe Torre was nominated but not confirmed as his replacement. Dr. Niederhuber added that Panel members are considered special government employees and therefore must meet many requirements; Mr. Torre's appointment was not confirmed because of these and scheduling conflicts. Dr. Niederhuber said he attended a meeting about the PCP with the White House staff member responsible for Presidentially-appointed committees; the size of the Panel was discussed, as was the issue of adding a member with star quality versus someone less well known.

Dr. Judith S. Kaur, Medical Director, Native American Programs, Mayo Comprehensive Cancer Center, and Professor of Oncology, Department of Medical Oncology, Mayo Clinic, questioned how it could be ensured that the public would view inclusion of every cancer patient as part of a national clinical trial as a positive goal, and how this could be prevented from increasing disparities, because those who participate in the national programs are more likely to receive the newest and best treatments. Dr. Leffall responded that physicians must be more successful in communicating that the trials are beneficial, because he still sees many patients who fear that they will be experimental subjects. Dr. Niederhuber added that he had attended a meeting with the NCI Director's Consumer Liaison Group on NCI's vision of drug development; the group's goal was to understand the vision and how it could impact the changing risk of cancer, and its response was enthusiastic. Dr. Niederhuber will continue to hold discussions with this group, which will provide another method for the NCI to communicate with the public.

V. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), reported on appropriations, Congressional hearings, meetings with members of Congress, and legislation of interest.

Appropriations Status. The House and Senate bills have yet to be reconciled; a continuing resolution is in effect until 18 December 2009 and likely will be extended. As they stand, the House bill allocates $5.15 B to the NCI, while the Senate bill allocates $5.05 B.

Congressional Hearings. The NCI offered input on the topics of two Congressional hearings held during the fall on the health effects of cell phone use and breast cancer legislation addressing screening in younger women. Dr. Steve Taplin, Screening Research Branch, NCI's Division of Cancer Control and Population Sciences (DCCPS), served as a witness at the breast cancer hearing, and NCI staff assisted with NIH testimony (given by the National Institute of Environmental Health Sciences [NIEHS]) at the cell phone hearing.

Meetings With Members of Congress. Drs. Helman and Rosenberg of the NCI gave presentations to a large group of House Members who visited the NIH on October 6, 2009. Senator Jon Tester (D-MT) spoke at an NCI Innovative Molecular Analysis Technologies meeting on October 8, 2009,

toured the clinical center, and attended presentations by Drs. Helman and Staudt. NCI staff also participated in briefings on scientific collections, prostate cancer research, and childhood cancer research at the House of Representatives.

Legislation of Interest. Provisions relevant to the NCI in the current health care reform bills include those relating to comparative effectiveness research (CER), a term which is being used interchangeably with "patient-centered outcomes research." Two strategies are under consideration: creating a center for CER within the Agency for Healthcare Research and Quality (House bill), or creating a nonprofit non-governmental organization to conduct the research (Senate bill). Additionally, two issues related to the Small Business Innovation Research (SBIR) program are included in current legislation. A law was passed 30 October 2009 providing a temporary extension of the SBIR program through 31 January 2010. To address the need for long-term reauthorization of the SBIR program, HR 2965 was introduced in the House that would extend the program through 2011 and also would increase the set-aside for the program. A Senate bill (S. 1832) would include SBIR set-aside in the ARRA: the bill removes NIH's exemption from set aside for ARRA and requires the NIH to obligate $150 M of its ARRA funding to SBIR.

VI. ANNUAL REPORT: AMERICAN ASSOCIATION FOR CANCER RESEARCH— DR. TYLER JACKS

Dr. Tyler Jacks offered an overview of the AACR's scientific scope, impact on cancer research, and perspectives on today's scientific opportunities and challenges. AACR's mission is to prevent and cure cancer through research, education, communications, and collaborations, and its membership includes researchers, physicians, survivors, advocates, and students in 89 countries. AACR integrates all fields relevant to cancer research, and hopes to promote the connection among basic, clinical and translational, and prevention research.

AACR's publications include *Cancer Research*, the oldest English language cancer publication in the world. Its journals receive more than 11,000 submissions annually, and received 20 percent of total oncology citations in 2008. In addition, its annual meeting will be attended by more than 15,000 people; it will be held in Washington, DC, in 2010, and educational sessions will cover a range of cancer research topics. AACR held additional conferences in 2009, including New Frontiers in Basic Cancer Research and numerous special scientific conferences.

AACR's goals in science policy and legislative affairs include: education of legislators, policymakers, and the media about the value of cancer research; communication of the economic opportunities in cancer research; advocating for increased funding; working with the FDA to accelerate drug approval; and emphasizing the human and economic cost of cancer. AACR's efforts in survivor and patient advocacy include engaging the survivors and family members in all aspects of AACR's work and facilitating their access to accurate cancer information.

Current challenges in drug development include difficulty in delivering effective drugs to patients; only 5 percent of cancer drugs that enter Phase I clinical testing get approved by the FDA. How to select the right targets, drugs, and patients for testing, needs to be understood, because the large investment required to have a success rate of this low percentage is unsustainable. Most pharmaceutical industries are shifting their research and development out of their own laboratories and into the academic setting; therefore, cancer research in academia is even more important. The revolution in genomics will assist in improvement of the drug discovery process. Cancers occur in context, in interaction with other cells in the body that influence the molecular changes and behavior of the disease. Biologists have been inadequately prepared to deal with the complexity, because they have been trained to consider very linear signaling pathways. The areas of systems biology and computational and mathematical modeling have emerged to meet cancer's complexity. RNAi therapeutics is another important emerging area. Cancer cells are highly

diverse in their nature, with many mutations and genomic alterations. Many of the genes that are affected are "undruggable targets," but RNAi offers the opportunity to control the activity in any gene regardless of the coded protein's function. RNAi molecules cannot be delivered effectively to cancer cells yet, but with new technologies and nanotechnologies, that may be possible. Nanotechnology will impact cancer research, and the NCI deserves credit for recognizing the importance of this emerging area. Additionally, new imaging agents are being developed to locate cancers at earlier stages and diagnose them more effectively. Cancer research is experiencing an enormous growth in the amount of available data, which will require infrastructure to manage and use the information most effectively, and the field is expanding to meet these challenges.

Questions and Answers

Dr. Coffey noted that the AACR served as a perfect model of a professional society in terms of its work with the NCI and ability to stay on the cutting edge of cancer research, and its successes should be studied so that they can be replicated with other cancer societies. To address the inefficiency in the development and approval of medical oncology drugs, he suggested that the AACR and the NCI incorporate both theoretical oncology biology and engineering. Dr. Jacks responded that the NCI has begun the process, and the AACR's membership likewise is broadening to include engineering disciplines, but the collaboration of scientists and engineers must be promoted.

Ms. Giusti noted that the AACR is a trusted third party in cancer research, in large part because of CEO Dr. Margaret Foti's outreach efforts. She encouraged the AACR to become involved with data management and analysis and legal issues to help overcome delays in the drug approval process. Dr. Jacks responded that taking on the volumes of data is of interest to the AACR. The AACR has held discussions about how it could work to overcome the legal and other issues surrounding the drug approval process, especially those involving combination therapy, use of drugs from different companies, or accessing drugs for academic research.

Dr. H. Kim Lyerly, Director, Duke Comprehensive Cancer Center, and George Barth Geller Professor of Cancer Research, Duke University Medical Center, acknowledged AACR's support and sponsorship, along with the American Society of Clinical Oncology, of the FDA workshop on the drug approval process, and AACR's support of the Asia Pacific Clinical Oncology Research Development workshop; he asked about AACR's vision of the future of academic researchers in cancer. Dr. Jacks responded that the most effective institutions today and in the future will have, either in their own institutions or through institutional interactions, a range from basic cancer research through translational research.

Dr. Hong commented that funding and public confidence are needed to translate discoveries from basic research to cancer patients, and asked how the AACR intended to continue the momentum from the success of the Stand Up to Cancer initiative. Dr. Jacks responded that with respect to Stand Up to Cancer, Dr. Foti's efforts produced $110 M in cancer research funding overseen by the AACR in this new team-oriented science concept. AACR is optimistic that there will be additional funding through that mechanism, and other organizations may be inspired to work with the AACR through its success.

Mr. William H. Goodwin, Jr., Chairman and President, CCA Industries, Inc., asked for further information on the inflow and outflow of AACR's funds. Dr. Jacks agreed to provide this to the Board.

Dr. Pietenpol noted that key to the success of the AACR and the NCI is their unwavering commitment to stellar and cutting-edge research, and she shared Dr. Jack's concern about inadequate future funding for cancer research. The NCI and associations such as the AACR working together allowed a turnaround of 2 years for a fusion protein, ELC, from discovery to use in patients, and that would not

have been possible without all the genomic discoveries; the funding outlook may not allow such a fast turnaround again. Dr. Niederhuber thanked Drs. Jacks and Foti for all of their work.

VII. OPERATIONAL EFFICIENCY WORKING GROUP INTERIM REPORT: BARRIERS TO TIMELY ACTIVATION OF CLINICAL TRIALS—DR. GABRIEL N. HORTOBAGYI

Dr. Gabriel Hortobagyi, Chairman, Department of Breast Medical Oncology, and Director, Breast Cancer Research Program, The University of Texas M.D. Anderson Cancer Center, provided a report on the Operational Efficiency Working Group's (OEWG) efforts in streamlining the operations of the NCI clinical trials system. The OEWG was established following recommendations from the Clinical Trials Working Group (CTWG) and the Clinical Trials and Translational Research Advisory Committee (CTAC). Composed of 63 clinical trial stakeholders, the OEWG is working to expedite trial activation, particularly by gathering consensus on key barriers, committing to achieve new target timelines and develop new process maps, identifying external factors that delay activation, establishing firm dates to terminate protocol development, and developing recommendations and implementation plans.

Dr. Hortobagyi next described efforts to improve the process for Cooperative Group Phase III trials, Cancer Center investigator-initiated trials, and Investigational Drug Branch (IDB) early drug development Phase II trials. Between FY 2006 and 2008, only 2 percent of Cooperative Group Phase III trials were activated in less than 1 year, 40 percent took 1 to 2 years, and 58 percent took more than 2 years; in addition, the majority of protocols (58 out of 69) underwent two to four revisions. The proposed OEWG timeline is to reduce the process to 300 days, and a two-pronged strategy to achieve this includes action plans for: 1) specific Cooperative Groups to consider potential staffing changes, trial development steps performed in parallel, coordinated interactions to resolve issues, and a protocol tracking and management tool; and 2) the Cancer Therapy Evaluation Program (CTEP) to coordinate scientific and clinical reviews to identify issues during concept and protocol reviews, streamline communication, and develop a project management/protocol tracking tool. Other recommendations include constructing a process for concept and protocol revision, as well as developing approaches to reward performance against timelines. An important component was the decision to terminate protocol development for proposals not activated within 24 months of concept submission.

The OEWG's proposed timeline for Cancer Center investigator-initiated trials is 90 days from protocol review to Institutional Review Board (IRB) approval. A Center-specific action plan to achieve the OEWG target timeline includes identifying potential plan elements (e.g., writers and resolution of differences), developing timeline targets, explicitly allowing use of Cancer Center Support Grant (CCSG) funds for protocol development, and providing supplemental funds to implement the action plan. Moreover, the university contracting and financial review processes should be streamlined at both the system and institutional levels.

Dr. Hortobagyi told members that the proposed OEWG timeline for the IDB early drug development Phase II trials reduces the time to activation to 210 days, with protocols terminated if they are not activated within 18 months. Recommendations involve a CTEP action plan that includes teleconferences and improved communication methods, and also a process for letter of intent (LOI) and protocol revision.

A number of process improvements are applicable across trial categories, including: the standardization of tools and templates to result in the rapid assembly of protocols; prioritization of Cancer Center trials to better use resources by reducing the number of protocols in development; and enhancement of biomarker funding and capabilities to help accelerate the rapid activation of trials that involve critical biomarker studies. The OEWG also discussed the participation of Cancer Centers in Cooperative Group trials; strategic review of Cancer Center clinical trials; and clinical research mentorship and training. Dr. Hortobagyi recognized the aggressive nature of the goal to reduce the median trial time by as much as

one half. ARRA administrative supplements are being used to assist in this endeavor, but devoted incremental funding and other economic incentives will be necessary in the long term to ensure that the Cooperative Groups and Cancer Centers meet the new timelines. Future OEWG activities include the preparation of the Phase I OEWG Final Report and commencement of OEWG Phase II to address the rate of accrual and time-to-trial completion.

Questions and Answers

Dr. Runowicz requested further details about the implementation schedule. Dr. Doroshow explained that, with NCAB approval of the interim OEWG report, all work on Phase II trials that have been ongoing for 18 months and Phase III trials for 2 years would cease as of 1 January 2011. This deadline would provide the community a 1-year notice to meet the timetable. Dr. Doroshow said that the NCAB will receive the final written document at a later time.

Ms. Giusti asked about how the team incentives will work. Dr. Hortobagyi replied that in the ideal situation, central IRB approvals and activation by the Centers will occur within the timeframe; he said staff will monitor progress during the next 12 months to ascertain if any Groups or Centers are experiencing difficulty with the schedule. In a year, and after careful review of these data, positive and negative incentives will be implemented for Groups, Centers, and CTEP.

Mr. Goodwin and Dr. Runowicz sought further clarification about the timetable and funding. Dr. Linda K. Weiss, Cancer Centers Program (CCP), answered that the solicitation is forthcoming, with return applications due in January 2010; matched funding will cover approximately 30 supplements for Cancer Centers. Dr. Doroshow added that similar requests will be issued for Cooperative Groups and N01 contracts.

Dr. Lyerly congratulated Drs. Hortobagyi and Doroshow for their coordination of the streamlining activities. He asked about recognition programs for investigators who have been instrumental in trial successes but did not serve as a Principal Investigator (PI) on an NCI-recognized clinical trial, and also about the accountability of Cooperative Group chairs and committee leaders. Dr. Doroshow observed that the NCI recently handed the first 11 NCI clinical trials team leadership awards at a translational research meeting, which were specifically for investigators whose efforts ensured the opening of major multidisciplinary trials. Dr. Hortobagyi added that accountability is a review criterion for Cooperative Groups. Dr. Lyerly suggested that a merit-based prioritization score be given at the Cancer Center level and that the use or description of the scientific priority score be revisited to prevent misinterpretation that could affect investigator careers. Drs. Hortobagyi and Linda Weiss, Cancer Centers Program, noted the variability in the Cancer Centers' approach to prioritization and told members that the OEWG recommendations include the development of a uniform evaluation system and scoring system within each Center to ensure transparency.

Dr. Hong said that the clinical trial process in other countries often occurs within 2 years, and he suggested that the NCI might adopt some lessons from their efficiency. Dr. Hortobagyi commented that pertinent information could be derived from the U.S. pharmaceutical industry as well.

Dr. Kaur suggested that the NCI should consider the types and numbers of clinical trial groups needed to conduct clinical trials most effectively. Dr. Hortobagyi agreed and said that the steering committees and other stakeholders will help determine this.

Dr. Coffey emphasized the importance of encouraging medical oncologists, and he suggested that the success or failure of a drug trial likely influences the careers of oncologists; he expressed interest in hearing about this. Dr. Hortobagyi said that the research encompasses all of the oncology specialties, and

that analyses of successes and failures have been discussed in literature, including the well-known papers by Drs. Dilts and Sandler.

A lengthy discussion ensued about the approval of the interim draft report and timetable. The interim draft report was not provided in written form to the Board and thus could not be approved in motion. Mr. Goodwin proposed a motion to approve the target dates as requested in concept but subject to a final review of the written report in February 2010; following extensive discussion, Mr. Goodwin withdrew the motion. Dr. Diana M. Lopez, Professor, Department of Microbiology and Immunology, University of Miami, Leonard M. Miller School of Medicine, made a motion to defer the vote on the report and reschedule it for the NCAB meeting in February 2010, allowing time for the Board's review. During the discussion, Dr. Coffey asked that the report be carefully reviewed by a Board member with expertise in the clinical trials process. Dr. Lyerly agreed to serve as this reviewer and provide to NCAB a summary of advantages and challenges of the report recommendations and proposed timeline. He expressed his reluctance to approve a document without appropriate time for comments or feedback. Dr. Doroshow said that the CTAC expressed its support for the report. Dr. Runowicz summarized the discussion by noting that the Board will receive a copy of the report before the February 2010 NCAB meeting, and a Subcommittee meeting of those who practice in the Cooperative Groups, Cancer Centers, and other clinical groups will be held the evening prior to the Board meeting.

Motion. A motion was made to vote on the proposed time limits for clinical trials at the February meeting, after receipt and review of the draft OEWG report. The motion was seconded and approved unanimously.

VIII. CENTER FOR CANCER RESEARCH STATUS REPORT—DRS. ROBERT WILTROUT, SHIV GREWAL, SHYAM K. SHARAN, PATRICIA STEEG, LOUIS STAUDT, AND W. MARSTON LINEHAN

Introduction. Dr. Robert Wiltrout, Director, Center for Cancer Research (CCR), provided an overview of the Center, which is an internal arm of the NCI that integrates basic, translational, and clinical research to make cancer preventable, curable, or chronically manageable. The CCR has developed scientific centers of excellence for its work in bench-to-bedside translation in immunology, chromosome biology, HIV and cancer virology, molecular oncology, and genitourinary malignancies, as well as integrated cancer biology and genomics. The Center reflects the NCI's emphasis and approaches to personalized medicine and is investing in programs that bolster discovery and accelerate translation. Dr. Wiltrout told members that during President Obama's tour of the NIH campus in September 2009, he met with Dr. W. Marston Linehan, Chief, CCR Urologic Oncology Branch, and discussed hereditary kidney cancer and advances being made in the CCR. CCR laboratories and branches are woven around strategic priorities, including the interrogation of the molecular genetics of cancer, the topic for today's presentations. Dr. Wiltrout next introduced the speakers: Drs. Shiv Grewal, Head, Chromosome Biology Section, Laboratory of Biochemistry and Molecular Biology; Shyam K. Sharan, Head, Genetics of Cancer Susceptibility Section, Mouse Cancer Genetics Program; Pat Steeg, Head, Women's Cancer Section, Laboratory of Molecular Pharmacology; Louis Staudt, Head, Molecular Biology of Lymphoid Malignancies Section, Metabolism Branch; and W. Marston Linehan.

Questions and Answers

Mr. Goodwin asked about the CCR's budget. Dr. Niederhuber replied that the budget for the NCI intramural program of $400 M is approximately 10 percent of the NCI's overall budget. Dr. Lloyd K. Everson, Vice Chairman and Member of the Board of Directors, US Oncology Incorporated, queried about the recruitment of CCR patients. Dr. Niederhuber said that patients with rarer cancers come from around the world, but for more common tumor types, the majority of patients may come from more local regions.

RNA-Mediated Epigenetic Control of the Genome. Dr. Grewal said that understanding how higher order chromatin structure and appropriate transcription is maintained has implications for cancer research. Chromatin modifiers, such as histone deacetylases, and RNA processing factors suppress transcriptional "noise" across the genome; accumulation of aberrant RNAs can lead to genomic instability, a hallmark of cancer. RNAi and chromatin modifying factors silence unwanted transcription and help maintain genomic integrity.

Saccharomyces pombe has been used as a model system to study chromatin maintenance and transcriptional suppression and shares a number of chromatin modification pathways with humans. The *S. pombe* genome encodes centromeric protein B (CENP-B) that binds to repeat elements distributed across the genome. CENP-Bs suppress transcription from these elements; deletion of CENP-Bs results in upregulation of retrotransposon transcription and subsequently genetic instability. CENP-Bs recruit chromatin modifiers such as the multienzyme effector complex, SHREC, and histone deacetylases to repress retrotransposons transcription and protect genome integrity. SHREC facilitates positioning of nucleosomes across the genome to maintain a repressed chromatin structure that prevents aberrant transcription and recombination. The histone deacetylases and related proteins recruited by the CENP-Bs also participate in heterochromatin silencing; mutations in some of these proteins, such as HP1, have been observed in certain cancers.

A large proportion of the *S. pombe* genome, including the intergenic regions, is transcribed in both directions. Genome-wide suppression of antisense RNA is maintained by the variant histone H2A.Z and the RNAi machinery. H2A.Z is found at the 5N end of genes; loss of H2A.Z results in gradual accumulation of antisense transcripts. H2A.Z acts synergistically with the histone methyltransferase protein Clr4 and the RNAi factor Ago1 to suppress antisense transcripts. Northern blot analysis found that these antisense transcripts result from read-through from a correctly transcribed gene into an adjacent gene that is positioned in the reverse orientation, rather than deriving from new initiation events.

This work has demonstrated that H2A.Z and AgoI are part of an RNA quality control mechanism that suppresses antisense transcription. Together with the CENP-B proteins, these two mechanisms maintain genomic integrity and prevent aberrant transcription that could lead to carcinogenesis.

Questions and Answers

Dr. Coffey asked whether Dr. Grewal had examined the role of metabolism and energy balance in these processes because energy balance can affect the activities of some histone deacetylases. Dr. Grewal answered that the histone deacetylase that is affected by metabolism is not found in yeast. Dr. Coffey asked whether Dr. Grewal had examined the effects of DNA looping on maintenance of genomic integrity by this system. Dr. Grewal answered that CENP-Bs bind to retrotransposons and silence transcription locally but also can facilitate coiling of the DNA into clusters that help to maintain DNA stability. Treatment of the cells with hydrogen peroxide causes the clusters to open and retroelement transcription is initiated; he currently is working to determine if this is a general stress response. CENP-Bs also bind replication origins and other associated factors with roles in initiating and terminating DNA replication.

Understanding the Functional Significance of Variants Identified in Human Breast Cancer Susceptibility Genes. Dr. Sharan reminded members that breast cancer is one of the most common malignancies in women, with 200,000 new cases diagnosed each year. Of these, between 10,000 and 14,000 are familial breast cancer cases, most often associated with mutations in BRCA1 and BRCA2. The risk of breast cancer for U.S. women in the general population is 13.7 percent, versus 35 to 85 percent for BRCA1 and BRCA2 mutations carriers; carriers also have a significantly increased risk of ovarian cancer. BRCA1 and BRCA2 function as tumor suppressor genes that are involved in maintaining genomic integrity and repairing DNA damage. BRCA1 has a RING domain that has E3 ligase activity and also BRCT repeats that may function in transcriptional activation. BRCA2 interacts with RAD51, which is a

key DNA repair protein. Mutations have been identified throughout the coding and noncoding regions of BRCA1 and BRCA2. Many of these mutations (24% for BRCA1 and 47% for BRCA2) result in single amino acid changes, many of which are neutral. Understanding how significantly these mutations raise an individual's risk of developing breast cancer is difficult, and there are no functional assays for BRCA1/BRCA2 activity. A study conducted by Myriad Genetics found that among 10,000 individuals, 17 percent of those with a history of breast and ovarian cancer had clearly deleterious BRCA1/BRCA2 variants, but 13 percent had variants of unknown clinical significance. The heterogeneity of BRCA1/BRCA2 mutations causes difficulties for counseling patients about their risk of developing breast or ovarian cancer.

To better understand the risk posed by BRCA1/BRCA2 variants, a functional assay using mouse embryonic stem (ES) cells was developed. BRCA1 and BRCA2 are essential for ES cell viability; ES cells also can maintain a stable genome, which is important when analyzing genes involved in DNA repair. Because the mouse and human genes are only 60 percent identical, bacterial artificial chromosomes (BACs) containing either human BRCA1 or BRCA2 (whole genomic region including regulatory elements) were used to engineer single nucleotide changes and examine the effects of these changes on gene function. Heterozygous ES cells in which one copy of BRCA2 was disrupted and the other functional allele could be conditionally disrupted were created. BACs containing the variant of interest are introduced into the cell and the functional allele is disrupted. If the cell does not survive, the BRCA2 mutation is presumed to be deleterious. BAC complementation also was performed to demonstrate that wild-type BRCA2 could rescue these ES cells. This work identified several variants that were lethal, and presumably would be associated with high risk for breast cancer, but also found other variants (termed "hypomorphs") in which the cells were viable, but hypersensitive to DNA damaging agents. This assay could be used to quantitate the ability of the BRCA2 variants to repair DNA damage induced by gamma radiation.

Two BRCA2 variants with mutations (arginine to glutamine and arginine to tryptophan) in the C terminal oligo binding domain of BRCA2 were examined in detail. Substituting tryptophan for arginine resulted in complete destabilization of the oligo binding domain, whereas the glutamine variant is predicted to retain 60 to 80 percent of wild-type activity. Both variants conferred a hypersensitivity to DNA damaging agents, but the damage observed was primarily an increase in translocation rather than massive genomic instability. These results suggest that these variants could be considered low risk and cancer prevention decisions made accordingly. To determine whether this assay is physiologically relevant, BRCA1 variants found to be associated with significantly increased cancer risk in the human population were transfected into ES cells, and embryos were derived from the cells. Several of these variants were embryonic lethal; another variant resulted in viable mice with no cancer observed for nearly a year. Work is in progress to express these variants in mammary gland to determine if they cause tumorigenesis in this tissue.

The assay may be useful for providing information that can be used in the clinic. In one case, a BRCA2 variant that was truncated at amino acid 3309 was identified in an individual diagnosed with ovarian cancer at age 32. The patient's sisters also had these variants and wanted to know their risk of developing ovarian cancer. Testing this variant in the ES cell assay showed that it behaved as a deleterious variant, providing the women with specific information regarding their risk. ES cells thus provide a simple and tractable system to study the function of BRCA1 and BRCA2 variants. Efforts are underway to examine variants from family linkage studies in this system to further demonstrate the clinical relevance of the assay.

Questions and Answers

Dr. Everson asked whether Dr. Sharan had access to clinically relevant BRCA1 and BRCA2 variants. Dr. Sharan answered that he is working with Myriad Genetics to mine their family linkage studies

and validate the activity of BRCA1 and BRCA2 variants found in these families. The Breast Cancer Information Core database lists BRCA1 and BRCA2 variants that also can be tested in the system.

Dr. Pietenpol asked whether any of the variants identified in the ovarian cancer analysis performed by TCGA had been analyzed. Dr. Sharan replied that work was in progress to analyze variants with mutations in the C terminus of the BRCA2 protein.

Dr. Coffey asked if Dr. Sharan had analyzed the effects of balanced versus unbalanced chromosome changes on ES cell viability because cancers with balanced changes often have better prognoses. Dr. Sharan said this analysis has not yet been conducted.

Brain Metastasis of Breast Cancer: Molecular and Preclinical Advances. Dr. Steeg described preclinical work to prevent and treat brain metastasis of breast cancer. The incidence of brain metastases in any cancer is about 170,000 a year, which is 10-fold higher than primary brain tumors, and breast cancer is second only to lung cancer as a leading cause of brain metastasis. Brain metastases are most prevalent in metastatic patients with either triple negative (ER-, PR- and HER2-) or HER2+ tumors. Standard treatments currently include surgery or stereotactic radiation, and both cause neurocognitive deficits and adversely affect quality of life. Treatment of brain metastases also is complicated by the inability of most chemotherapeutics to cross the blood-brain barrier. The blood-brain barrier consists of endothelial cells that are connected by continuous tight junctions and express multiple efflux pumps; additional barrier functions are provided by a basement membrane, pericytes, and the feet of astrocytes. Although large metastases were thought to compromise the blood brain barrier, studies of fluorescent particle uptake have shown that the barrier remains intact even in the presence of most very large lesions. Similar studies showed distinct and heterogeneous patterns of relatively low uptake of radiolabeled paclitaxel and doxorubicin, which are frequently used in breast cancer therapy but are ineffective against brain metastases.

A mouse model system for brain metastasis of breast cancer was established using MDA-MB-231, an aggressive triple negative breast cancer cell line. Brain metastatic variant cells were injected into the left cardiac ventricle of mice, ensuring delivery to the brain; brain metastases were isolated, grown in culture, and reinjected to isolate the 231-BR brain-seeking cell. Large metastases and micro-metastases were characterized histologically, and proliferation, apoptosis, and the neural inflammatory response were examined and found to be similar to that of human brain metastases, suggesting that this is a valid model in which to explore treatments for human breast cancer brain metastases.

The HER2 pathway is amplified in 25 percent of breast cancers and is active in brain metastasis, leading to efforts to deliver drugs targeting this receptor to the brain. The humanized monoclonal antibody to HER2, trastuzumab (Herceptin®), has been effective in combination with chemotherapy for treatment of metastatic breast cancer, but has been less successful for treating HER2+ brain metastases. One study found that 25 percent of 93 metastatic patients receiving Herceptin® had brain metastases; this was the sole metastatic site in 69 percent of the patients, and 50 percent of these patients died from brain metastatic lesions. To examine whether *HER2* over-expression itself influenced the development of brain metastases, 231-BR cells were transfected with a vector that over-expressed *HER2* and injected into mice. Three-fold greater large brain metastases formed, suggesting that *HER2* over-expression promotes brain metastatic colonization. Lapatinib, an orally available tyrosine kinase inhibitor that is fairly permeable to the brain, was tested in an attempt to prevent brain metastasis in these mice. Micrometastases in the brain were unaffected, but a 53 percent decrease in large metastases was observed. Lapatinib was tested in humans and did not prevent brain metastases, but use of lapatinib in combination with capecitabine in the metastatic setting appears promising to prevent brain relapse.

Comparison of gene expression patterns in brain metastases versus primary tumors showed that 80 percent of the differentially percent genes are down-regulated in the metastatic lesions. This led to efforts

to re-activate the genes using a histone deacetylase inhibitor with proven blood-brain barrier permeability. Treatment of mice injected with 231-BR cells with vorinostat resulted in a decrease in the large metastases and also in micrometastases when administered early in the course of the disease. Contrary to its expected mechanism of action, vorinostat induced double-stranded breaks in DNA and thus may increase the efficacy of radiation therapy.

This research was supported by both the NCI Intramural program and a grant from the Department of Defense Breast Cancer Research Program.

Questions and Answers

Dr. Hong asked whether the combination of vorinostat and lapatinib has been studied with or without chemotherapy in the animal model systems. Dr. Steeg answered that these two have not been studied together but other combination studies are in planning, including a kinase inhibitor that is brain permeable.

Dr. Lyerly asked whether biological differences between small and large metastases have been found at the level of gene or protein expression. He also asked whether mutations in the metabolic enzyme IDH (1 and 2) have a role in metastases. Dr. Steeg replied that small and large metastases have not been profiled for their differences, but the idea is intriguing. Additionally, her laboratory has not focused on IDH; hexokinase 2, however, is upregulated in brain metastases, and *in vitro* data suggest a relation with cell viability under hypoxic conditions.

Dr. Lyerly asked about strategies for drug delivery in brain metastasis, such as through direct delivery pumps and reservoirs. Dr. Steeg indicated that such approaches have not been successful, but new strategies for drug delivery are in development and may prove more effective.

Dr. Pietenpol observed that identifying similarities in the patterns of triple negative breast cancer and *HER2* subgroups, tumors which have very different biologies, might suggest important therapeutic targets.

In response to a question from Dr. Kaur concerning data about the subgroup that overexpresses both HER2 and ER and efforts to manipulate upregulation of HER2+ tumors that lose ER, Dr. Steeg indicated that data are available; gene expression patterns are being examined and subset signatures are being generated.

RNA Interference Screens and Cancer Gene Resequencing To Discover the Achilles Heel of Cancer. Dr. Staudt described efforts to define diffuse large B cell lymphoma (DLBCL) subtypes and how this work can effect the development of therapies. Gene expression profiling identified three DLBCL subtypes: 1) activated B cell-like (ABC); 2) germinal center B cell-like (GCB); and 3) primary mediastinal B cell lymphoma. ABC DLBCLs have the poorest prognosis, with a 3-year progression free survival of only 40 percent using current standard chemotherapy compared to 75 percent for GCB.

The NFκB pathway is aberrantly activated in ABC DLBCL, leading to uncontrolled cell proliferation. IκB kinase is constitutively active in these cells, causing inactivation of IκB, which then cannot inhibit NFκB. RNAi screening, in which thousands of genes can be inactivated and genes necessary for survival of cancer cells identified, was used to identify the signaling mechanism upstream of IκB kinase that constitutively activates this kinase in ABC DLBCL. *CARD11*, which encodes a signaling scaffold protein, was found to be permanently activated in ABC DLBCL cells. Phosphorylation of CARD11 activates MALT and BCL10, which in turn activate NFκB. Somatic mutations in the CARD11 coiled-coil domain were found in 10 percent of ABC cells. These coiled-coil domain mutants form cytoplasmic aggregates that colocalize with NFκB signaling components and activate NFκB.

RNAi screening was used to identify the lesion responsible for proliferation and survival of the 90 percent of ABC DLBCLs that do not have *CARD11* mutations. This screen found that *BTK*, which is required for B cell receptor signaling, is necessary for survival of ABC cells with wild-type *CARD11*. BTK initiates downstream signaling in the B cell receptor (BCR) signaling pathway. Knockdown of the CD79 component of the BCR was toxic to ABC DLBCL cells with wild-type *CARD11*. Sequencing analysis found no mutations in *BTK*, but did identify mutations in CD79A and CD79B ITAM motifs that alter receptor tyrosine kinase activity. CD79B was preferentially mutated in ABC DLBCL cells; 21 percent of these cells either have mutations in the tyrosine residue of ITAM or have an ITAM deletion. The chronically active BCR signaling that occurs because of the acquisition of CD79B/A mutations is responsible for DLBCL pathogenesis, as it results in increased clonal expansion and NFκB signaling.

Because activation of NFκB occurs by different mechanisms in ABC DLBCL, different therapeutic strategies for treating subsets of ABC DLBCL are needed. Cells with mutated *CARD11* could be treated with IKKβ inhibitors, proteasome inhibitors, or neddylation inhibitors. Cells with chronic active BCR signaling could be treated with BTK inhibitors, SRC family inhibitors, SYK inhibitors, or PKCβ inhibitors. Dasatinib is known to block BCR signaling, and treatment with this drug blocked phosphorylation activity and killed ABC DLBCL cells with constitutively active BCR signaling and wild-type *CARD11*, but not cells with mutant *CARD11* or GCB DLBCL cells.

A clinical trial was conducted to test whether inhibiting aberrant NFκB activation would be useful in treating this cancer. The proteasome inhibitor bortezomib, which blocks IκB degradation, was used to inhibit NFκB activity. Initially, the results of this trial were not impressive because the drug was tested in DLBCL patients without specifying subtypes. When the results were analyzed by subtype, a response was observed in approximately 80 percent of ABC DLBCL patients, but only in approximately 13 percent of GCB patients. This work emphasizes the importance of molecular profiling to more effectively treat lymphoma. To this end, the Lymphoma/Leukemia Molecular Profiling Project was created by the NCI in 1999 and has as its goal the implementation of a molecular diagnosis of lymphoma in routine clinical practice.

Genetic Basis of Kidney Cancer: Opportunity for Disease-Specific Targeted Therapy. Dr. Linehan told members that analysis of familial kidney cancer syndromes has helped identify a number of genes involved in renal carcinogenesis. Categorizing kidney cancers by histologic and genetic type has improved diagnosis, treatment decisions, and outcome predictions. Dr. Linehan described five familial kidney cancer syndromes: 1) Von Hippel Lindau (VHL) syndrome; 2) Hereditary Papillary Renal Carcinoma (HPRC); 3) Birt Hogg Dubé (BHD) syndrome; 4) Hereditary Leiomyomatosis Renal Cell Cancer (HLRCC); and 5) Succinate Dehydrogenase Familial Renal Carcinoma (SDFRC). The genetic defects involved in each of these cancers have been identified and all affect fundamental metabolic processes.

VHL syndrome is characterized by clear cell carcinomas, as many as 600 tumors per kidney. Tumors also develop in the adrenal glands, pancreas, brain or spine, eyes, and inner ears. Nephron-sparing enucleation is used to manage this cancer, with surgery delayed until the largest renal tumor is at least 3 cm in diameter; the surgery usually can be performed laparoscopically. The *VHL* gene is located on chromosome 3 and was mutated in nearly 100 percent of VHL families, as well as in 92 percent of sporadic clear cell RCC, the most common type of sporadic kidney cancer in the United States. Mutations in the *VHL* gene interfere with normal degradation of hypoxia inducible factor-1α (HIF-1α and HIF-2α) in normoxic cells. Accumulation of HIF leads to activation of growth factor receptors such as the vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and epithelial growth factor (EGFR). Targeting pathways modulated by these growth factors has improved survival for clear cell RCC patients.

HPRC kidney tumors are type I papillary renal carcinomas. Similar to VHL, this condition also is managed by nephron-sparing enucleation when tumors are larger than 3 cm. HPRC arises from activating mutations in the tyrosine kinase domain of *MET* that can be found in the germline of HPRC patients. The effectiveness of a dual VEGF-MET inhibitor is being evaluated for treatment of this form of renal cancer.

BHD syndrome includes cutaneous lesions (fibrofolliculomas) and lung cysts as well as kidney tumors. Kidney tumors in BHD comprise chromophobe, oncocytoma, and oncocytic- hybrid types. Surgical management of BHD is similar to that of HRPC and VHL. The BHD gene is located on chromosome 17 and is mutated in 94 percent of BHD families; mutations are found throughout the gene, and 97 percent of the mutations result in frameshifts or a truncated protein. Most tumors found in the kidney of a single BHD patient have a different somatic mutation. Folliculin (the product of the BHD gene) functions in the mTORC pathway, which is involved in energy and nutrient sensing. Mice with homozygous deletions in the BHD gene in the kidney die at 30 days from renal failure, but their lifespans can be doubled by rapamycin treatment. Preclinical experiments in which mTORC1 and mTORC2 activation is blocked show promise for treating this renal cancer.

HLRCC is characterized by cutaneous and uterine leiomyomas, along with highly aggressive renal cell carcinomas. The syndrome is inherited in an autosomal dominant fashion. Unlike VHL, HPRC, and BHD, even small HLRCC tumors are often removed immediately because of the aggressive nature of this cancer. HLRCC is caused by mutations in the gene-encoding fumarate hydratase (FH), a Krebs cycle enzyme. Mutations in *FH* lead to accumulation of fumarate, which blocks HIF-1α degradation. The syndrome also is characterized by reactive oxygen species generation,and high rates of glycolysis in the tumor cells. HIF-1α targets become upregulated in HLRCC kidney tumors and targeting VEGFR/EGFR in advanced HLRCC resulted in some responses.

Mutations in another Krebs cycle enzyme, succinate dehydrogenase, have been linked to a familial pheochromocytoma and kidney cancer. Inactivation of the genes encoding succinate dehydrogenase can inactivate the enzyme and lead to accumulation of succinate and subsequently higher HIF-1α levels.

Histologic analysis has shown that renal cancer consists of different types of diseases, and linkage analysis of familial forms of renal cancer has identified the genes responsible for these kidney cancer types. A number of these genes are involved in metabolism, including oxygen sensing, iron balance, and nutrient sensing, suggesting that kidney cancer can be considered to be a metabolic disease.

Questions and Answers

Dr. Coffey recalled that attempts had been made to block glycolysis in kidney tumors, but this also resulted in adverse effects on the brain from the drop in glucose levels. He asked whether blocking glycolysis while locally administering glucose to the brain could be effective. Dr. Linehan agreed that this might be possible, but because the tumors are highly vascular, it might not be possible to deliver sufficient 2-deoxyglucose to block glucose metabolism. Dr. Coffey complimented Dr. Linehan on the extensive amount of information known about kidney cancer subtypes and carcinogenic mechanisms. He said that the characterization of kidney cancer as a metabolic disease should lead to a number of promising leads for therapy. Dr. Linehan agreed and noted that the pharmaceutical industry is testing compounds that target processes such as proteasome degradation and HIF-1α translation, as well as evaluating agents similar to metformin as potential approaches to treat cancer. Dr. Atala also complimented Dr. Linehan on his work, which has led to better targeted treatment of the different types of kidney cancer.

Dr. Kaur asked what could be learned from the process of dedifferentiation by chromophobes. Dr. Linehan indicated that progression appears to be from oncocytoma to chromophobe, but he has not studied this directly.

Dr. Pietenpol asked if retrospective studies of patients taking metformin for diabetes had been performed to determine if this affected kidney cancer risk. Dr. Linehan answered that this had not yet been done, but might be interesting, particularly because risk for uterine and kidney cancer is thought to be related to body mass index. Dr. Pietenpol asked if *MYC* deregulation was involved in the high levels of glycolysis observed in HLRCC. Dr. Linehan answered that this had not been determined, but *MYC* has been found to be amplified in a cell line derived from this cancer.

IX. 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 552(b)(c)(6), Title 5 U.S. code and 10(d) of the Federal Advisory Committee Act, as amended (5U.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.

X. DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS STATUS REPORT—DRS. JOSEPH FRAUMENI, JR., NATHANIEL ROTHMAN, LAURA BEANE FREEMAN, AND QING LAN

Introduction. Dr. Joseph Fraumeni Jr., Director, Division of Cancer Epidemiology and Genetics (DCEG), explained that the three following presentations would offer examples of work the DCEG has been conducting in the area of occupational and environmental epidemiology and its impact on public policy. Exposure assessment is the greatest challenge in occupational and environmental studies as it is often conducted retrospectively with indirect measures of exposure, and low levels may be difficult to detect. Other challenges include the study of interactions between the exposure and the host as well as the process of cancer risk assessment. Occupational cancer is a special focus of study because workers have greater exposures to specific carcinogens than the general population. Its study has led to the discovery of many human carcinogens, it provides opportunities for the discovery of mechanisms, and it serves as a sentinel for lower levels of exposure and risk in the general population. The NCI is conducting cohort studies of occupational exposures to several chemicals with public health importance such as benzene, formaldehyde, diesel exhausts, and pesticides, as well as radiation among radiological technologists, nuclear workers and other exposed groups. DCEG studies of exposures in the general environment include indoor and outdoor air pollution, ionizing and non-ionizing radiation, and water pollution (e.g., arsenic and nitrates). The studies to be discussed take advantage of "natural experiments" occurring due to exposures to benzene, formaldehyde, and indoor air pollution. Dr. Fraumeni then introduced the session speakers: Drs. Nathaniel Rothman, Senior Investigator, Occupational and Environmental Epidemiology Branch (OEEB), DCEG, NCI; Laura Beane Freeman, a tenure-track Investigator, OEEB, DCEG, NCI; and Qing Lan, a recently tenured Senior Investigator, OEEB, DCEG, NCI.

Benzene Exposure and Risk of Leukemia and Lymphoma. Dr. Rothman noted that the studies to be discussed were conducted with collaborators in China and with investigators at several universities in the United States. The work has played a role in the risk assessment process carried out by other federal agencies and has had an impact on environmental regulatory policy.

Benzene, at very high levels of exposure, causes acute myelogenous leukemia (AML), hematotoxicity, and possibly non-Hodgkin lymphoma (NHL). Several million workers are exposed to benzene in developed and developing countries, and almost the entire population is exposed to low benzene levels from gasoline and environmental tobacco smoke. A joint NCI- China Centers for Disease Control cohort study found that risks of AML and myelodysplastic syndrome (MDS) were elevated in workers exposed to less than 10 ppm of benzene, as well as an overall increased risk of NHL and lung cancer. Occupational benzene exposure limits in China were lowered in great part because of this study from 13 ppm (8-hour time-weighted average) to about 2 ppm in 2002. The U.S. occupational standard is 1 ppm benzene, and controversy exists regarding whether this is a safe level. Other questions concerning benzene include: the health risk from environmental exposure to benzene; whether it causes cancers other than AML; and its mechanisms of action and the role of genetic susceptibility.

A molecular epidemiology study in Tianjin, China, was conducted to evaluate benzene's effects in workers exposed to less than 1 ppm. The study conducted exposure assessment with monitoring badges and urine tests in 250 healthy shoe manufacturing workers exposed to benzene from two factories and 140 unexposed controls, and found that all major peripheral blood cells were decreased in workers exposed to less than 1 ppm of benzene. Additionally, myeloid progenitor cells (in particular CFU_GEMM and CGU_GM) were more sensitive than mature cells to benzene exposure, which suggests that mature cell counts in peripheral blood may underestimate benzene's hematotoxic effects. Genetic susceptibility to benzene toxicity also was examined; individuals who carried particular variants in genes that play key roles in activating benzene were at higher risk for having a lower white blood cell count at less than 1 ppm benzene exposure than those without the variant. Immediate clinical consequences of these subtle hematologic effects may not be evident, but the hematotoxicity may be associated with future risk of hematologic malignancies.

These studies provide new evidence linking benzene to lymphoma, refine our understanding of effects at low exposure levels, and help to reveal benzene's mechanisms in hematologic malignancies. Based on a review of studies conducted by investigators at NCI and other institutions, the U.S. Environmental Protection Agency (EPA) made a rule in 2007 to lower the benzene content allowed in gasoline, and in October 2009, a World Health Organization-International Agency for Research on Cancer's (WHO-IARC) Working Group concluded that there is additional limited evidence that benzene causes acute and chronic lymphocytic leukemia, NHL, and multiple myeloma. The approach used in the molecular epidemiology study of benzene can serve as a model for studying the biologic plausibility that other occupational exposures may cause cancer.

Questions and Answers

Dr. Karen M. Meneses, Professor and Associate Dean for Research, University of Alabama at Birmingham, School of Nursing, asked if there had been any changes in occupational health for the Chinese workers in the study. Dr. Rothman responded that environmental monitoring data have been used to make workplace improvements to reduce benzene exposure.

Dr. Coffey asked if benzene compounds affect sex characteristics in fish or other organisms. Dr. Rothman responded that some work suggests that benzene can affect sperm. Dr. Niederhuber noted that this study provided a tremendous opportunity to get genomic information at the point of risk, and would be a very fruitful area to mine in a similar way to TCGA. Dr. Rothman added that biological samples were collected using a fairly extensive protocol, and once relevant genes are identified, they can be examined for altered methylation patterns and other mutations that may allow identification of early events and future risks. Dr. Coffey questioned whether it is possible to detect the DNA- adducts and monitor them in patient samples. Dr. Rothman responded that benzene weakly binds to DNA, but has a greater affinity for certain amino acids, so albumin from blood samples can be monitored for protein adducts and there is a clear exposure-response relationship.

Dr. Steven Kleeburger, Acting Deputy Director, NIEHS, asked if any other candidate genes have been investigated in the cohort. Dr. Rothman replied that because of the understanding of the pathogenesis of leukemia and lymphoma, the investigators were able to develop a list of candidate genes and have had success investigating them.

Dr. Everson asked if formaldehyde and benzene levels in anatomy departments had been examined. Dr. Rothman commented that this is an ideal population to study and said that Dr. Beane Freeman would be discussing formaldehyde studies.

Formaldehyde Exposure and Risk of Nasopharyngeal Cancer and Leukemia. Dr. Beane Freeman explained that formaldehyde is ubiquitous in the atmosphere and in living organisms. In 1995, it was estimated that approximately 2.1 million U.S. workers were occupationally exposed to this chemical. Environmental exposure is likely to be more prevalent. The U.S. occupational standard set by the Occupational Safety and Health Administration is 0.75 ppm for an 8-hour time-weighted average, and 2 ppm for short-term exposure. Formaldehyde is genotoxic and causes DNA-protein crosslinks at the site of contact. In the early 1980s, studies showed that inhaled formaldehyde caused nasal tumors in rats. At that time a number of studies were initiated at the NCI and elsewhere to examine the effects of formaldehyde in humans. One such study initiated by the NCI was a cohort study of industrial workers. This mortality study included 25,619 workers who were employed prior to 1966 in 10 plants that used and/or produced formaldehyde. Investigators collected work histories and used historical records to construct a variety of exposure metrics, including peak formaldehyde exposure. Mortality information, including date and cause of death has been obtained through death certificates and linkage to the National Death Index. As of 2004, there were 13,951 deaths among the members of the cohort. Nasopharyngeal cancer is a very rare cancer; however, in this large cohort study, there were 8 exposed cases, all of which were in the highest peak exposure category, leading to a significant exposure-response trend. In addition to the large industrial cohort, a series of mortality studies of professionals who were exposed to formaldehyde (such as embalmers and pathologists) were conducted in the 1980s. These surveys consistently found that these groups had higher mortality due to leukemia and other lymphohematopoietic malignancies than the general population. However, early reports from industrial settings were not conclusive. Recently, the industrial cohort was updated with mortality data through 2004; the most recent publication from the study showed an increased risk of lymphohematopoietic malignancies with increasing peak exposures to formaldehyde. The results are somewhat stronger for myeloid than other types of leukemia.

Another study of occupational formaldehyde exposure was conducted among workers in the funeral industry. In this study, 6,808 deaths were identified among inactive or deceased funeral directors and embalmers. Of those, 268 deaths were due to lymphohemopoietic malignancies, including 34 from myeloid leukemia. To assess exposure, interviews were conducted with next of kin and coworkers to obtain work histories and characteristics of embalmings conducted. In addition, an exposure study monitored 25 embalmings under controlled conditions. These measurements were used to create models to predict formaldehyde levels under various conditions. Results of this study showed a three-fold increase of myeloid leukemia for the longest duration of embalming, the most number of embalmings performed, and the highest cumulative exposure to formaldehyde. This was the first study to relate cancer risk to work practices in the funeral industry.

The association between formaldehyde and leukemia has been relatively controversial, because formaldehyde is highly reactive and almost completely deposited in the upper respiratory tract. A molecular epidemiology study of formaldehyde in Guangdong, China, was designed to evaluate formaldehyde's toxic effects on bone marrow by studying 43 workers currently exposed to 1 to 2 ppm formaldehyde and 51 unexposed controls. Results showed a decrease in all cells derived from myeloid progenitor cells, along with an elevation of leukemia-specific chromosome changes in the myeloid progenitor cells, which suggests that formaldehyde may cause toxic effects in bone marrow of exposed

workers. The findings support the biological plausibility of an association between formaldehyde and leukemia.

The work conducted by the NCI on formaldehyde contributed to the WHO-IARC Working Group finding in 2009 that sufficient evidence exists to support formaldehyde's association with leukemia (myeloid leukemia in particular) and nasopharyngeal cancer. An Outside Expert Panel convened by the National Toxicology Program Report on Carcinogens in 2009 also determined that formaldehyde causes myeloid leukemia and nasopharyngeal cancer in humans. EPA is currently updating its risk assessment of formaldehyde, which will serve as a basis for its regulatory action.

Questions and Answers

Dr. Marie Sweeney, Chief, Surveillance Branch, Division of Surveillance Hazard Evaluation and Field Studies, National Institute for Occupational Safety and Health (NIOSH), noted that occupational safety and health epidemiology has progressed significantly during the past 30 years, and she suggested that the NCI should record work histories of individuals as these data are difficult to acquire and code, but are important to include in electronic health records and databases.

Dr. Kaur asked if the Epstein-Barr virus (EBV) was included as a co-carcinogen or multiplier factor, and wondered whether formaldehyde had been a co-carcinogen in the cases from Alaska, which has a preponderance of nasopharyngeal cancer incidence. Dr. Beane Freeman responded that information on EBV was unavailable for this cohort study. However, a case-control study of nasopharyngeal cancer conducted by another DCEG investigator, Dr. Alan Hildesheim, found that the association between formaldehyde exposure and nasopharyngeal cancer was stronger among those who were seropositive for EBV.

Dr. Niederhuber stated that he was struck by the difference in lymphoid and myeloid leukemia; it would seem that both progenitors would have the same type of susceptibility, and cases of aplastic anemia must be present. He asked about the power of the cohorts to drive understanding of the biology of the mechanisms. Dr. Beane Freeman noted that the studies that she had presented were based on death certificate data, so investigators were limited in their ability to examine the mechanisms more deeply in these studies. Dr. Rothman added that biologic samples have provided an important opportunity for mechanistic studies, including examining underlying genetic susceptibility and gaining insight into relationships between specific chemicals and conditions. He noted that the levels of formaldehyde that would cause aplastic anemia may be too irritating to be tolerated.

Indoor Air Pollution From Coal Combustion and Lung Cancer. Dr. Lan noted that 800 million people use coal in their homes worldwide, and indoor air pollution from solid fuel use is the eighth largest risk factor for global disease. Lung cancer mortality rates in Xuanwei are among the highest in China. Xuanwei is a rural county with a very stable population in which the majority of males are smokers while less than 0.1 percent of females are smokers. It therefore provides a unique opportunity for investigating lung cancer and indoor air pollution.

The investigators' initial work included: a cohort study on the impact of stove improvement on lung cancer risk; a case-control study on coal type and lung cancer; and a molecular epidemiology case-control study on the impact of genetic variation in lung cancer risk and potential interactions with smoky coal and polycyclic aromatic hydrocarbons (PAHs). The cohort study reported that after fire pits were replaced with chimney stoves to reduce exposure to coal combustion products in the study population, incidence rates of lung cancer and chronic obstructive pulmonary disease (COPD) decreased significantly, showing strong evidence of a causal association between smoky coal exposure and lung cancer and COPD.

The population-based case-control study was designed to evaluate the association between coal type and lung cancer risk. Results showed that lung cancer risk varies markedly by coal type, and limited air monitoring data provided evidence that coal emissions with the highest PAH levels were associated with increased lung cancer risk. The molecular epidemiology case-control study was designed to study genetic variation and its impact on lung cancer risk, and was the first epidemiologic study to collect biological samples (buccal cells and sputum) in the region. A gene involved in detoxification of PAHs, *GSTM1*, affected lung cancer risk for those exposed to smoky coal. *GSTM1*-positive subjects had a risk of 1.2-fold per 100 tons of smoky coal use, while those with *GSTM1*-null genotype showed a 2.4-fold risk per 100 tons.

Research findings contributed to the WHO-IARC Working Group decision to classify indoor emissions from coal combustion as carcinogenic to humans, and are being used to develop WHO Guidelines for Indoor Air Quality, as well as to support improved home ventilation and replacement of coal with cleaner sources of heating and cooking. To answer remaining questions, such as the exposure-response relationship between PAHs and other exposures present when coal is burned and lung cancer, a hospital-based case control study of lung cancer among never-smoking women was initiated in 2006. The exposure assessment goal was to characterize indoor exposure to key components of coal combustion products that may contribute to lung cancer risk. For example, personal and area air $PM_{2.5}$ and PAHs, as well as dermal and dietary PAH exposures/ co-exposures were measured. This study will be completed in 2010, and investigators will: estimate exposure to PAHs and particulates, genotype single nucleotide polymorphisms (SNPs) in key genes important for PAH metabolism and lung cancer etiology, and analyze the main effects of PAH exposure and co-exposures and interactions with genetic variants. A project is also under way to broadly assess the etiology of lung cancer among never-smoking females in Asia in a consortium of lung cancer studies involving about 6,000 cases and 6,000 controls; approximately 50 percent have used coal for cooking or heating. Data gathered will be used to better estimate exposure-response relationships between coal use, other sources of indoor air pollution, and the risk of lung cancer among nonsmokers, as well as susceptible subgroups. Findings should help to further develop environmental regulatory policy.

Questions and Answers

Dr. Hong asked if the multinational consortium study would be sponsored by the NCI, and recommended that investigators ensure that biospecimens are collected to examine the EGFR mutation status of the tumor and to analyze chromosome 2 in female nonsmokers, which has been shown to manufacture a protein that causes abnormal tumor growth. Dr. Lan responded that the consortium will be supported by the NCI. A number of these studies have included tumor specimen collections, and plans are being made to examine EGFR mutations. Consideration also will be given to analyzing variation in chromosome 2. In addition, a genome-wide scan of the cases and controls is being planned. Dr. Fraumeni added that in Asian countries the rates for lung cancer in nonsmoking women are the highest in the world, primarily for adenocarcinomas, and environmental exposures contribute in the form of indoor air pollutants. Genetic susceptibility also appears to play a major role, so the consortium study provides a tremendous opportunity to examine gene-environment interactions in lung cancer. Dr. Niederhuber asked if secondhand smoke effects will be taken into account, and Dr. Fraumeni assured that they would.

Dr. Anna Barker, Deputy Director for Advanced Technology and Strategic Partnership, noted that the amount of smog in China is significant, and asked if the studies accounted for this, and if the consortium study was powered for all the confounding factors. Dr. Rothman responded that a key component of the consortium is that studies are under way in many different parts of Asia with varying levels of pollution, and investigators can look for effects of the environment in different populations. Results will be adjusted for potential confounding factors and the study is suitably large to be able to take this into account.

Dr. Pietenpol asked about the data applicability to the United States, particularly factors that lead to lung cancer in never smoking women in the United States. Dr. Lan responded that the exposure-response relationship observed in studies in Asia could be used in the United States for cancer risk assessment, and the study of genetic susceptibility will translate well, including disentangling the effects of lung cancer susceptibility from the genetic determinants of smoking behavior. Dr. Pietenpol asked whether there has been a similar study of lung adenocarcinomas in U.S. never smokers. Dr. Rothman replied that there is ongoing work, although it is challenging to identify and enroll thousands of female never smokers with lung cancer.

Dr. Coffey asked Dr. Fraumeni to comment on the safety of nanoparticles. Dr. Fraumeni noted that this is a concern, as nanoparticles represent a source of particulate exposures. In particular, many nanoparticles occur in the form of tubules that resemble asbestos fibers, so that occupational studies in the manufacturing of nanoparticles will be extremely important in determining whether they pose a safety risk.

Dr. Michael A. Babich, Directorate for Epidemiology and Health Sciences, Consumer Product Safety Commission (CPSC), noted that in the United States, two kinds of coal are used and more people burn wood than coal, and asked if it would be possible to extrapolate the study's dose response to other combustion sources. Dr. Lan noted that the differences in composition of the coal in the United States versus China will be evaluated and that ashes, coal, and air samples have been collected from the ongoing study for a detailed analysis and comparison. Dr. Fraumeni added that some of the coal that is used in China is laced with arsenic.

Dr. Kleeburger asked whether, in the exposure assessments, investigators will be measuring endotoxins in the home; early exposures to these innate immune stimulating agents may be important in predisposing to or even protecting against the development of cancers. An NIH gene/environment interaction assessment consortium has developed novel exposure assessment tools that may be of some interest to investigators, and NIEHS is funding a number of studies on nanotechnology safety. Dr. Lan noted that blood samples have been collected, which can be used to measure endotoxins. Environmental samples were also collected, which can be combined with detailed information that was collected by questionnaire to evaluate endotoxin exposure and interactions with genetic markers. Dr. Fraumeni added that several studies have consistently reported that workers exposed to textile dust have lower risk of lung cancer than the general population, and the difference may be associated with endotoxin levels.

Dr. Lyerly commented that international collaborations are important, but asked how investigators could be supported in carrying out studies such as these in U.S.-relevant populations. Dr. Fraumeni discussed the current emphasis at NIH and NCI on global health and encouragement for undertaking studies in developing and other countries where scientific and public health opportunities exist for collaborative projects. Although the studies discussed are funded intramurally, the NCI is developing international programs that should facilitate work by extramural as well as intramural investigators. Dr. Niederhuber added that study sites in different countries provide unique exposures, and that diseases unique to certain areas of the world may inform the understanding of disease biology.

XI. TOBACCO REGULATION UPDATE—DR. CATHY BACKINGER

Dr. Cathy Backinger, Chief, Tobacco Control Research Branch, DCCPS, NCI, described FDA efforts to regulate tobacco products from 1994-2000 and the new law giving FDA regulatory authority over tobacco products. In 1996, the agency issued a Final Rule asserting jurisdiction over tobacco products. In 2000, the agency's jurisdiction was overturned by a Supreme Court decision which determined that the agency did not have the authority to regulate tobacco products. In February of 2007, the Family Smoking Prevention and Tobacco Control Act to grant FDA authority to regulate tobacco products was introduced in the 110th Congress; the bill was reintroduced in the 111th Congress, passed by

both the House of the Representatives and the Senate, and signed into law by President Barack Obama on June 22, 2009.

The new law provides FDA with broad authority to regulate the manufacturing, marketing, and sales of tobacco products. Specific provisions of the law include: restricting marketing and sales to youth; banning misleading descriptors including "light," "mild," and "low-tar;" requiring larger warning labels using graphic images; banning candy and fruit-flavored cigarettes; requiring brand-specific disclosure of ingredients; granting FDA the authority to set product standards to regulate harmful constituents, including nicotine; and enhancing states' ability to enact tobacco control laws in certain domains. The law also establishes a Tobacco Products Scientific Advisory Committee, expected to hold its first meeting in early 2010. Future research needs will include: addressing how changes in tobacco product design and smoking behavior moderate emissions, actual human exposure and harm; assessing the contributions of constituents of tobacco products to addiction and harm; developing new measures, including biomarkers, to determine the impact of tobacco product changes; understanding the impact of new warning labels and changing marketing practices on consumers' perceptions of tobacco products.

Dr. Robert Croyle, Director, DCCPS, has been named the NIH liaison to the FDA on tobacco product regulation; Dr. Croyle and other NIH staff have presented on this topic at numerous meetings. In 2003, the NIH Tobacco and Nicotine Research Interest Group was formed to increase collaboration, coordination, and communication on tobacco and nicotine-related research across NIH. The group includes representatives from across the NIH and from numerous other government agencies. In October 2009, NCI, CDC, and NIDA co-sponsored the "Second Conference on Menthol Cigarettes." Research presented at the meeting showed that menthol cigarettes are a starter product for youth, and are marketed specifically to youth, women, and African Americans. Also in October 2009, NCI convened a workshop on cigarette warning labels and packaging. Tobacco product warning labels used in other countries are larger, more graphic, and more effective than those currently used in the U.S. Research on tobacco warning labels and packaging, including studies funded by NCI, is ongoing, and will likely inform FDA implementation of the warning label provisions of the legislation. NCI's additional work in this area includes commissioning, with CDC, a series of White Papers to identify research needs from the new law, through the Society of Research on Nicotine and Tobacco, and collaborating with the World Health Organization on a joint monograph on tobacco product regulation.

Some of the provisions of the WHO Framework Convention on Tobacco Control (FCTC) are similar to the provisions of the FDA law. While the U.S. has not ratified the FCTC, it may be sent to the Senate for ratification at a future date. FDA regulation of tobacco products must be considered in the context of a comprehensive tobacco control and prevention program, including attention to smoking cessation, tobacco-related health disparities, global tobacco control, and activities of the newly established HHS Interagency Tobacco Control Working Group. For example, one recent NCI-funded research study found that proactive, personalized telephone counseling demonstrated a prolonged effect on quitting among adolescent smokers, and a recent comparative effectiveness study of smoking cessation medications found nicotine patch and nicotine lozenge combined had a significantly higher abstinence rate at 6 months compared to placebo.

Questions and Answers

Dr. Niederhuber noted that the NCI's work was a good example of its investment in and leadership of tobacco control efforts.

Dr. Kaur commented that the presentation showed the need for greater smoking cessation efforts for lower socioeconomic status smokers in targeted communities, and asked about NCI's strategy to meet the challenge of new nicotine and tobacco products being marketed. Dr. Backinger responded that the NCI would discuss these issues with the FDA. She also noted the need to implement systems that can be nimble

in their response to new products, that questions need to be added to some of the national surveys, and panels need to be developed to examine questions related to new products to respond quickly to the changing marketplace.

Dr. Champion suggested that the NCI should support research on relapse prevention. Dr. Backinger agreed that such research is needed.

XII. NCAB ONGOING AND NEW BUSINESS—DR. CAROLYN D. RUNOWICZ

Cancer Centers Subcommittee Report. Dr. Lyerly reported on the NCAB Cancer Centers Subcommittee meeting held on 30 November 2009. The meeting focused on understanding CER within the landscape of the Cancer Centers Program. Dr. Lyerly informed members that Dr. Croyle provided a presentation on CER, ARRA funding, and opportunities for the future. The Subcommittee requested periodic updates on the issue, dissemination to the NCAB of Dr. Croyle's presentation, and examples of potential opportunities for CER, such as those involving the Veteran's Administration (VA), health maintenance organization (HMO) Cancer Research Network (CRN), and the NCI Surveillance, Epidemiology and End Results (SEER) network. The NCI was encouraged to consider the Cancer Centers Program as a powerful tool to support CER. In addition, teleconferences between the NCI and Cancer Center directors should be held to update the directors about CER and foster ongoing dialogue about CER opportunities. Dr. Lyerly expressed appreciation for the efforts by Drs. Croyle and Weiss to coordinate this meeting.

Motion. A motion was made to accept the summary report of the 30 November 2009 Cancer Centers Subcommittee meeting. The motion was seconded and approved unanimously.

Establish New Subcommittee. Dr. Runowicz introduced Dr. Joseph Tomaszewski, Deputy Directory, DCTD, and Executive Secretary, NCAB *Ad hoc* Subcommittee on Experimental Therapeutics. Dr. Tomaszewski informed members that a Pharmacodynamics and Therapeutics Functional Working Group is proposed for establishment under the NCAB *Ad hoc* Subcommittee on Experimental Therapeutics. He said that a process has been underway to help the DCTD determine which molecular pathways and targets to concentrate on in the development of pharmacodynamic and pharmacogenomic assays for preclinical and early concept clinical trials; the overall goal is to fully validate assays at an early stage (i.e., stages 0 or 1) to support a decision about continuation in the clinic. The Working Group is a formalization of this process and will allow the NCI to bring extramural experts into the discussions. NCI staff will identify participants and share the list with the Board.

Motion. A motion was made to approve the creation of the Pharmacodynamics and Therapeutics Functional Working Group. The motion was seconded and approved unanimously.

Future Agenda Items. Dr. Runowicz described several topics for future Board meetings and invited members to provide suggestions. Recommendations for future meeting agendas included an update on the Community Clinical Oncology Program (CCOP), overarching landscape of NCI's funding history and mid-term outlook, the Specialized Program of Research Excellence (SPORE), and NCI's training efforts.

XIII. 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 152nd regular meeting of the NCAB was adjourned at 11:36 a.m. on Wednesday, 2 December 2009.

Date	Carolyn D. Runowicz, M.D., Chair
Date	Paulette S. Gray, Ph.D., Executive Secretary