DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
154TH NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
June 22–23, 2010

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

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
Summary of Meeting
June 22–23, 2010

The National Cancer Advisory Board (NCAB) convened for its 154th regular meeting on 22–23 June 2010, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, 22 June 2010, from 8:30 a.m. to 3:30 p.m., and Wednesday, 23 June 2010, from 8:30 a.m. until adjournment at 11:39 a.m., and closed to the public on Tuesday, 22 June 2010, from 3:30 p.m. to 5:00 p.m. The NCAB Chair, Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, Farmington, CT, presided during both the open and closed sessions.

NCAB Members
Dr. Carolyn D. Runowicz (Chair)
Dr. Anthony Atala (absent)
Dr. Bruce A. Chabner
Dr. Victoria L. Champion
Dr. Donald S. Coffey
Dr. Lloyd K. Everson
Ms. Kathryn E. Giusti (absent)
Mr. William H. Goodwin, Jr.
Dr. Waun Ki Hong
Mr. Robert A. Ingram
Dr. Judith S. Kaur
Mr. David H. Koch
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

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. Allen Dearry, 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. Jason Donaldson, 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, JUNE 22, 2010

WEDNESDAY, JUNE 23, 2010

TUESDAY, JUNE 22, 2010

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF 18 FEBRUARY 2010 MINUTES—DR. CAROLYN D. RUNOWICZ

Dr. Runowicz called to order the 154th 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: Dr. Phil Sharp, past NCAB Chair and member, who received the Margaret Foti award; Ms. Kathryn Giusti, CEO and Founder, Multiple Myeloma Research Foundation, Inc., who received the Harvard Business School's Alumni Achievement Award; Dr. Daniel Von Hoff, Physician in Chief and Senior Investigator, Translational Genomics Research Institute (TGen), Clinical Professor of Medicine, Department of Medicine, University of Arizona, who received the David Karnofsky Memorial Award; and Dr. John Niederhuber, Director, NCI, who received the Distinguished Public Service Award. Dr. Runowicz noted that Dr. Niederhuber accepted the award on behalf of the entire NCI.

Motion. A motion was made to approve the minutes of the 18 February 2010 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 2012.

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

Dr. John Niederhuber, Director, welcomed members and provided information about NCI's fiscal year (FY) 2010 and 2011 budgets, NCI's investments, planning for NCI's space needs for years ahead, facilitating therapeutic development, and messages from the Executive Committee (EC) scientific retreat.

Budget. Dr. Niederhuber informed members that the FY 2011 President's Budget (PB) proposal for the NCI is $5.26 B, which reflects a 3.1 percent increase over the FY 2010 operating budget of $5.10 B. American Recovery and Reinvestment Act (ARRA) funds to the NCI totaled $1.26 B in FY 2009-2010. Applications for grants in FY 2011 are estimated to reach a 16.8 percent success rate. However, after accounting for the increase in applications due to those that were not funded by the ARRA funds but are resubmitted and those for which 2-year ARRA funding will be ending, the success rate is estimated at 15.7 percent.

Dr. Niederhuber said that the NCI's FY 2010 budget is on track to close out without major issues. The EC continues to prioritize funding decisions within budget constraints, and weekly budget meetings monitor spending. FY 2010 competing research project grants (RPGs) are estimated at $496 M, nearly $40 M more than FY 2009 and almost 10 percent of the budget. Approximately $203 M has been set aside to fund requests for applications (RFAs), which is $70 M more than last year. Dr. Niederhuber told members that $317 M (25%) of ARRA funds committed in FY2010 will be obligated for grants and contracts in FY2011.

NCI's Investments. Dr. Niederhuber reminded members that, despite below-inflation budgets, the NCI has launched important initiatives during the past several years. These include: the Chemical Biology Consortium (CBC); Functional Biology Consortium (FBC); Physical Sciences-Oncology Centers; Coordinating Center for Clinical Trials (CCCT); cancer Biomedical Informatics Grid (caBIG®) Health Consortium; Target Discovery and Development Network; Advanced Technology Partnership Initiative (ATPI); Cancer Human Biobank (caHUB); and NCI Community Cancer Centers Program (NCCCP). The NCCCP's sites, which exist across the United States, provide easier access to NCI-sponsored treatment trials, use a clinical trials screening accrual log, and incorporate an informatics strategy (e.g., NCI's caBIG® tools). In addition, all NCCCP hospitals have patient navigators, and all sites are assessing how to adopt NCI's Best Practices for Biospecimen Resources. Members were informed that the NCCCP interfaces with a number of other NCI programs, including the NCI Cancer Centers Program, Community Clinical Oncology Program (CCOP), Community Network Program, Minority-Based (MB) CCOP, Cancer Trials Support Unit (CTSU), and The Cancer Genome Atlas (TCGA), among others.

Planning for NCI's Space Needs. Dr. Niederhuber provided details about the NCI's move in 2013 to the Shady Grove complex. The campus will include custom-built, state-of-the-art buildings with 490,000 net square feet of usable space, accommodating 2,400 staff members; the buildings will meet Leadership in Energy and Environmental Design's (LEED) silver rating. The site was selected following a rigorous, year-long competitive bidding process conducted by the General Services Administration (GSA) in consultation with the NIH and NCI. The location is close to Shady Grove Adventist Hospital, Johns Hopkins University, the University of Maryland, and several pharmaceutical and biotechnology companies.

Dr. Niederhuber also informed members that the Advanced Technology Research facility is a 330,000 square foot facility in Frederick, MD, that will contain NCI's Biopharmaceutical Development Program manufacturing facility, NCI's Advanced Technology Program, and administrative offices. The facility is sited strategically in a technology park to foster public-private partnerships with biotechnology and other companies. The facility was presented the 2010 Economic Development Award by the Maryland Economic Development Association.

Facilitating Therapeutic Development. Dr. Niederhuber began by stating most oncology drugs fail in late stages of development; 70 percent of cancer agents in Phase II fail to enter Phase III, and 59 percent that enter Phase 3 fail. A recent Institute of Medicine (IOM) report *A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program* recommends four goals: (1) promote consolidation and efficiency; (2) incorporate innovation in science and trial design; (3) provide adequate funding and support; and (4) incentivize participation by patients and physicians. Dr. Niederhuber said that the NCI clinical trials system must reflect the dramatic changes in cancer biology that have occurred during the past 20 years.

The NCI Experimental Therapeutics (NExT) Program has the mission to advance clinical practice and bring improved therapies to patients with cancer by supporting the most promising new drug discovery and development projects. NExT is a merger of NCI drug and imaging agent development programs and includes the integration of the Pharmacodynamics (PD)-Biomarkers Program and the creation of the Chemical Biology Consortium (CBC) and Functional Biology Consortium (FBC). The NExT application and review process involves four rounds annually; to date, three cycles have been completed: 52, 53, and 23 applications have been received for cycles 1, 2, and 3, respectively. NExT serves an important role in developing agents to targets defined by cancer genomic and functional biologic studies. Dr. Niederhuber further described patient characterization centers where tumor profiles can be used by practicing oncologists to improve diagnosis, disease management, and patient outcome. He posed the question "Where is the optimal integration of molecular cancer science and clinical research being conducted?" He suggested that the answer may lie in a single, national Cooperative Group trial structure that incorporates NCI Cancer

Centers, the Clinical Cancer Center Program, Patient Characterization Centers, NCCCP, CCOP, and perhaps a national clinical trial patient cohort.

NCI Executive Committee Scientific Retreat. Dr. Niederhuber reminded members that participants at the NCI's EC Scientific Retreat in January 2010 agreed that cancer should be analyzed as a network of systems and that multi-dimensional datasets will become standard. Drug and diagnostic development in an age of personalized medicine requires a new business model, and teamwork is critical for success. Other messages included embracing the complexity and heterogeneity of cancer and that nanotechnology is driving revolutionary advances. Better incentives for collaboration and tissue collection are needed. The NCI faces numerous challenges, including forming public-private partnerships, particularly around drug development; reshaping clinical trials; increasing or maintaining momentum created by ARRA; fostering innovative, collaborative scientific initiatives; and balancing citizenship and leadership responsibilities as an NIH Institute.

Questions and Answers

Mr. David H. Koch, Executive Vice President, Koch Industries, asked Dr. Niederhuber to share his thoughts about the use of the double blind clinical trial with improved survivability as a measure of success. Dr. Niederhuber indicated that the question under consideration should determine the type of trial to design. He added that many endpoints depend on the trial question, and different endpoints exist at different stages of a trial; other metrics in addition to longevity to determine the benefit of a therapeutic agent are quality of life and toxicity. Additional challenges include bringing the right patient with the right set of targets to the right drug recipe, and handling intellectual property and trade issues.

Dr. Bruce Allan Chabner, Clinical Director, Massachusetts General Hospital Cancer Center, and Chief of Hematology/Oncology, Massachusetts General Hospital, commented that issues include designing the new system and obtaining buy-in from members of the oncology community who are invested in the current system. Dr. Niederhuber agreed and said that approximately $150 M would provide the incentive to accelerate the community's change to a new system that allows smaller trials, more intense study of patients, and possibly imaging of the target in real time. Dr. James H. Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), echoed Dr. Niederhuber's comments and noted that, while large randomized trials may still be conducted in the future, technological advances will spur more effective processes; a milieu is necessary that allows investigations in which scientific and technology experts can interface in new ways with practitioners who have the appropriate patients for enrollment on the right trials.

IV. PRESIDENT'S CANCER PANEL REPORT—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 the NCI staff, in particular Dr. Abby Sandler, PCP Executive Secretary for the Panel, for assisting the PCP at this meeting. The Panel currently consists of Dr. Leffall and Dr. Margaret L. Kripke, who are awaiting White House appointment of a third Panel member. Dr. Leffall reminded members that the mission of the Panel is to monitor the development and execution of the activities of the National Cancer Program (NCP) and to report directly to the President. Any delays or blockages in rapid execution of the NCP are brought immediately to the President's attention.

The 2008–2009 Panel report *Reducing Environmental Cancer Risk: What We Can Do Now* was delivered to the White House in April and released to the public in May 2010. The report recommended: a prevention-oriented approach to environmental contaminants; an assessment of workplace chemicals and other exposures to quantify health risks; and promulgation and enforcement of regulations related to environmental exposures by agencies responsible for this, through an integrated, coordinated, and

transparent system. It also suggested strengthening research in epidemiologic and hazard assessment, acceleration in the development of measurement tools and exposure assessment research, and better understanding of the relationship between residential radon exposure and cancer risk. In addition, actions should be taken to minimize radiation exposure from medical sources, and the unequal burden of exposure to known and suspected carcinogens must be addressed. Other recommendations included that physicians should query patients routinely about workplace and home environments as part of the standard medical history, and products from "green chemistry" research should be well studied prior to and following their introduction into the environment. Public health messages should be developed and disseminated to raise awareness of environmental cancer risks.

The 2009–2010 meeting series covered the topic "America's Demographic and Cultural Transformation: Implications for the Cancer Enterprise." Meetings were held in Seattle, WA; Los Angeles, CA; Wilmington, DE; and Miami, FL. The Panel has begun preparing the 2009–2010 report and expects its release near the end of 2010.

Dr. Leffall informed members that the 2010–2011 meeting series "The Future of Cancer Research: Accelerating Scientific Innovation" is inspired by the 40th anniversary of the 1971 National Cancer Act. The meetings will attempt to better define the role of various stakeholders in the NCP and will reflect on past progress and consider the best direction for the future of cancer research and the NCP. The series also will consider how the cancer community can utilize a broad array of scientific, computational, and emerging disciplines to accelerate progress of the NCP. The meetings are scheduled for 22 September 2010 in Boston, MA; 26 October 2010 in Philadelphia, PA; 14 December 2010 in Bethesda, MD; and 1 February 2011 in Atlanta, GA. Specific topics that the meetings may explore include: changes in the cancer research and advocacy landscape since 1971; the vision for cancer research for the next 15 years; transformative changes and the technological revolution in cancer research; and medical, ethical, and legal issues, as well as barriers to advancing to a new era of cancer research.

Questions and Answers

Mr. Koch asked about the composition and format of the Panel meetings held across the country. Dr. Leffall said that the meetings involve stakeholders from cancer-related areas who present on their expertise, and the Panel members and public attendees ask questions to obtain the best possible information. The Panel also obtains additional information to expand or clarify specific topics after the meetings. Dr. Niederhuber added that audience members also offer their opinions, facilitating a public dialogue about cancer throughout the country.

Dr. H. Kim Lyerly, Director, Duke Comprehensive Cancer Center, and George Barth Geller Professor of Cancer Research, Duke University Medical Center, applauded the 2008–2009 Panel report on environmental cancer risk, noting that it is remarkable to bring cancer, environmental policy, and environmental science experts together, and he observed that the report has engendered considerable discussion. He wondered about the current status of this work. Dr. Leffall replied that the Panel responds to direct inquiries regarding the report but that the Panel does not have the authority to implement the recommendations found in the report. Dr. Leffall was pleased that there has been considerable public discussion of the report findings. Dr. Runowicz commented that obesity and tobacco remain at the forefront of environmental factors because they are major causes of cardiovascular disease and cancer.

Dr. Runowicz commented on Mr. Lance Armstrong's participation as a third member on the PCP, particularly his interest and knowledge about cancer and his ability to capture the imagination of youth and others; she expressed the hope that when a third member is appointed, he/she will bring similar qualities. Dr. Leffall agreed that Mr. Armstrong brought a positive force to the Panel. Dr. Judith S. Kaur, Medical Director, Native American Programs, Mayo Comprehensive Cancer Center, and Professor of Oncology, Department of Medical Oncology, Mayo Clinic, added that the Panel exerts a broad influence among the

public; she encouraged the NCAB to state for the record that the Panel is enhanced by having a public member.

Dr. Chabner asked about the Panel's interaction with President Obama and its ability to bring key cancer messages and other issues to the President's attention. Dr. Leffall said that the Panel provides reports to White House staff who inform the President. 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, wondered whether the NCAB has ever asked the PCP to convey a message to the President. The answer is that this has not been requested.

Dr. Runowicz encouraged the Panel to share synergistic pursuits in reference to its 2010–2011 subject matters and the charge of the NCAB *Ad hoc* Working Group to Create a Strategic Scientific Vision for the National Cancer Program and Review of the National Cancer Institute.

V. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), reported on appropriations, Congressional hearings, and legislation of interest. Ms. Erickson invited members to browse the OGCR Web site (http://legislative.cancer.gov) for additional details on these topics.

Appropriations Status. The PB was announced 1 February 2010, allocating to the NIH and NCI $32.09 B and $5.26 B, respectively. The House and Senate held hearings on the NIH budget in April and May 2010.

Congressional Hearings. The NCI provided testimony at several House Subcommittee hearings on prostate cancer screening and treatment, cancer research progress and challenges, and smokeless tobacco. Other cancer-related topics that Congress has asked about include: the NCI Cancer Centers Program; cancers in young adults and adolescents; xenotropic murine leukemia virus (MLV)-related virus; early cancer detection; genetic testing; and sunscreen.

Legislation of Interest. Provisions relevant to the NCI in the Patient Protection and Affordable Care Act (P.L. 111-148) include the Cures Acceleration Network (CAN), comparative effectiveness research (CER), breast cancer research in young women, and access to cancer clinical trials. The 21st Century Cancer Access to Life-Saving Early Detection, Research and Treatment (ALERT) Act (S. 717), which was introduced by the late Sen. Edward Kennedy (D-MA), remains under consideration in the Senate Health, Education, Labor, and Pensions (HELP) Committee; House Energy and Commerce Health Subcommittee members have indicated an interest in introducing a House companion bill.

Questions and Answers

In response to a question from Mr. Koch about the Protection and Affordable Care Act, Ms. Erickson clarified that insurance providers must provide reimbursement for routine costs associated with access to cancer clinical trials; the provision does not pertain to managers of clinical trials, who must operate trials in a proper scientific manner.

VI. RECOGNITION OF DEPARTING MEMBERS—DRS. JOHN NIEDERHUBER AND CAROLYN D. RUNOWICZ

On behalf of the NCI, Dr. Niederhuber recognized and thanked six NCAB members whose terms of office are expiring as of this meeting. For each, he provided a brief description of their particular contributions to the NCI over and above their service on the NCAB. The retiring members are: Dr. Lloyd K. Everson, Vice Chairman and Member of the Board of Directors, US Oncology Incorporated; Ms. Giusti;

Mr. Koch; Dr. Diana M. Lopez, Professor, Department of Microbiology and Immunology, University of Miami, Leonard M. Miller School of Medicine; Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center; and Dr. Daniel Von Hoff, Physician in Chief and Senior Investigator, Translational Genomics Research Institute (TGen), Clinical Professor of Medicine, Department of Medicine, University of Arizona. Dr. Runowicz also was thanked for her years of service and dedication as NCAB Chair.

VII. INSTITUTE OF MEDICINE REPORT: A NATIONAL CANCER CLINICAL TRIALS SYSTEM FOR THE 21st CENTURY—DRS. JOHN NIEDERHUBER, JAMES H. DOROSHOW, JOHN MENDELSOHN, AND HAROLD L. MOSES

Dr. Doroshow provided an overview of the IOM's report, *Changing the NCI's Clinical Trials System To Meet the Needs of the 21st Century*. He underscored the importance of the NCI clinical trials system to reflect the dramatic changes in cancer biology that occurred during the past 20 years. This system encompasses Cooperative Groups and networks, as well as national tumor banks, which work throughout the clinical trials spectrum, including available data and specimens, high priority trials, rapid protocol creation, Central Institutional Review Board (CIRB), central patient enrollment, and standard tools for trial conduct. Dr. Doroshow introduced the speakers: Drs. John Mendelsohn, IOM Committee Chair, M.D. Anderson Cancer Center; and Harold L. Moses, IOM Committee Vice Chair, Vanderbilt-Ingram Comprehensive Cancer Center.

Dr. Mendelsohn informed members that the Cooperative Group Program comprises 10 Groups with more than 3,100 institutions; 14,000 investigators; and an annual enrollment of 25,000 patients. Research from the Program has contributed to significant advances in the treatment and prevention of cancers such as multiple myeloma and childhood leukemia. Cooperative Group trials complement industry trials by addressing important questions that are less likely to be pursued by private industry. However, the Cooperative Group Program is at a critical juncture because the infrastructure of clinical trials has not evolved to accommodate the rapid pace of biological discovery. In particular, processes are inefficient and lack stringent prioritization, and government oversight is extensive and complex. Additionally, while funding has become stagnant, rising costs are expected as a result of biomarker-driven treatment selection in personalized medicine.

The IOM Committee provided several recommendations:

(1) Improve the speed and efficiency of the design, launch, and conduct of clinical trials. The NCI should consolidate the Cooperative Group's operations and prioritize management improvements, such as by consolidating the number of disease-site committees; by consolidating patient registration, data collection and management, and funding and reimbursement for patient accrual; and by streamlining protocol development. The Committee also encouraged the Department of Health and Human Services (HHS) to lead a transagency effort to streamline and harmonize government oversight and regulation of cancer clinical trials. NCI should facilitate more collaboration among cancer clinical trial stakeholders.

(2) Incorporate innovative science and design into cancer clinical trials. The NCI should mandate the submission of annotated biospecimens to high-quality, standardized central biorepositories. In addition, Cooperative Groups should lead the development and assessment of innovative clinical trial designs that evaluate cancer therapeutics and biomarkers. The NCI should establish a consistent, dynamic process to oversee the development of national unified standards for imaging and biomarker tests.

(3) Improve prioritization, selection, support, and completion of cancer clinical trials. The NCI should reevaluate its role in the clinical trials system; specifically, the Committee encouraged the NCI to file more investigational new drug (IND) applications for testing and to focus more on facilitating and supporting rather than oversight, and encouraged all the Scientific Steering Committees to deliberate

independently of NCI staff. The NCI, Cooperative Groups, and physicians should work to increase the speed, volume, and diversity of patient accrual and ensure high-quality trial performance. In addition, the NCI should allocate more resources to the Cooperative Group Program to ensure sufficient resources to achieve its mission.

(4) Incentivize the participation of patients and physicians in clinical trials. All stakeholders should ensure that clinical investigators have adequate training and mentoring, paid protected research time, necessary resources, and recognition. Moreover, health care payment policies should value the care provided to patients in clinical trials and adequately compensate for that care.

The IOM Committee agreed that clinical trials make tremendous contributions to improving cancer care; the processes for designing, opening, and completing clinical trials should become more efficient and streamlined, with more rigorous prioritization. All stakeholders, including clinical investigators, pharmacology and biotechnology companies, government, patients and advocates, and health care payers, share the responsibility of improved patient care and the need to collaborate on implementing the recommendations. The Committee also supported the idea that clinical trials should place increasing emphasis on innovative design, the use of biomarkers, and adequate funding. Finally, the value of designing and conducting clinical trials must be recognized by adequate reimbursement of costs. Dr. Mendelsohn informed members that the report is available online (www.nap.edu).

Questions and Answers

Dr. Moses noted that the process leading to the recommendations began 3 years earlier and involved two workshops on improving clinical trial quality and examining the cooperative groups. Mr. Koch characterized the IOM report as a thorough, stimulating study that could lead to a marked improvement in clinical trials. Comparing drug trials to the risks and benefits of oil exploration, he asked whether NCI adequately reviews the merit of risky trial proposals. Dr. Mendelsohn expressed the opinion that trial protocols undergo thorough evaluation and noted an aversion to risk, particularly at the U.S. Food and Drug Administration (FDA); currently, NIH's study sections are funding only 15 to 20 percent of trials. Dr. Von Hoff commented that Phase I trials are somewhat overregulated, and broader eligibility criteria are needed. Dr. Chabner suggested that NCI oversight can be excessive, even on the order of 120 days for NCI review of Phase III trials; he also noted that the existing Phase III trial timeline can consume 360 days at the NCI. Dr. Mendelsohn agreed and recommended that the NCI should facilitate but not oversee trials for which the Institute does not hold the IND. Dr. Chabner stressed the urgency of the changes needed across NCI and asked whether participation of the Cooperative Groups and their leadership can be obtained to achieve buy-in. Dr. Mendelsohn responded that groups are beginning to work together. Dr. Coffey asked about the reasons for delayed trial inception and steps that might prevent similar situations in the future. Dr. Mendelsohn responded that likely causes for delayed trials were perfectionism and desire for control on the part of various stakeholders in the planning process, and funding levels inadequate to cover costs; he added that site visits can provide an effective mechanism of control and that funding should pause or cease as a result of bad reviews. Dr. Lyerly asked about a vision for the future regarding auditing standardization and the relationship with industry. Dr. Mendelsohn replied that, in an ideal world, businesses and the NCI would have consensus on standardized procedures; the NCI has the ability to realize this goal at least in the public domain. An additional complication, however, is that multiple agents addressing different pathways and derived from different companies may be needed to cure one cancer.

Dr. Kaur suggested, in reference to IOM recommendations that mandate annotated biospecimens (Recommendation 5) and increase in the diversity of patient accrual (Recommendation 9), that emphasis should be placed on the education and outreach components to accomplish these goals, and she wondered whether sufficient consideration has been paid to this at both the academic and community levels. Dr. Mendelsohn answered that many academic centers have outreach programs and are reaching out to disparate populations. A growing concern, however, is that increasing numbers of trials will relocate to

Europe and China, where oversight is not as stringent as in the United States. The United States offers the advantage of access to large numbers of African American and Central and South American population groups that are not well represented in Europe and China; Dr. Mendelsohn noted that diverse population groups are critical in clinical trials.

Dr. Runowicz thanked Dr. Niederhuber for inviting the IOM co-Chairs to present to the Board and summarized the charges for the NCAB: the NCAB should have an increased role in advising NCI on fund allocation regarding national clinical trials and this process should commence immediately; NCAB also should provide guidance on a system to eliminate duplication, including consolidation of multiple groups as needed; NCI oversight should be examined, and the Institute should assume a facilitator role and eliminate its 120-day review as appropriate, consider a reduced number of Cooperative Groups, and streamline front- and back-end operations. Dr. Runowicz suggested that the NCAB should consider these recommendations at a future meeting.

Dr. Chabner noted that the IOM report contains a regular report on implementations. He suggested monitoring progress on implementations at every other NCAB meeting. Dr. Mendelsohn stated that collapsing infrastructure is a good solution but the disease sites should not be consolidated into one site; some competition is needed. Dr. Moses noted that the Cooperative Group principle works well as evidenced in the "volunteer army." Dr. Runowicz stated that the point would be to improve efficiencies and make processes more effective. Dr. Niederhuber said that it would cost money to implement recommendations; resources would need to be shifted to reimbursement, which presents challenges. Dr. Runowicz agreed that the NCI budget for Cooperative Groups is small, and additional funding may be needed as well as more efficient processes. Dr. Mendelsohn suggested that the NCAB could provide the necessary mandate for such increases. Dr. Chabner recommended that increases in funding should not precede the commencement of major changes.

VIII. OPERATIONAL EFFICIENCY WORKING GROUP REPORT (OEWG)—DR. JAMES H. DOROSHOW

Dr. Doroshow presented the report of the Operational Efficiency Working Group (OEWG), which was established by the Clinical Trials and Translational Research Advisory Committee (CTAC) to recommend strategies and implementation plans for reducing the activation time for Cooperative Group and Cancer Center trials. The 63 members of OEWG represent a broad spectrum of stakeholders, including all 10 Cooperative Group Chairs and eight Cancer Center Directors. Dr. Doroshow informed members that the OEWG assessed Cooperative Group Phase III trials, Cancer Center investigator-initiated trials, Investigational Drug Branch (IDB) early drug development Phase II trials, and Cancer Center activation of Cooperative Group trials. The OEWG developed a commitment to new target timelines for steps, as well as new process maps, in trial activation, along with recommendations and associated implementation plans to achieve these timelines. The Working Group also established firm dates to terminate protocol development if all issues are not resolved.

Dr. Doroshow said that analysis of Cooperative Group Phase III trials from 2006 to 2008 found that 40 percent of trials took 1-2 years for activation and 58 percent took more than 2 years. In addition, most protocols underwent 2-4 revisions. The OEWG's target timeline of 300 days includes 90 days each for concept receipt to approval and approval to protocol submission, which are reduced from the median times of 93 and 138.5 days, respectively. The targeted time from protocol submission to approval is 120 days, reduced significantly from the average 348.5 days. Recommendations to achieve these improvements included: development of a group-specific action plan and a Cancer Therapy Evaluation Program (CTEP) action plan to achieve the target timeline; creation of a Collaborative Group/CTEP process for concept and protocol revision; and developing approaches to reward performance against timelines.

For IDB early drug development Phase II trials, the analysis showed that 61 percent of trials took 1-2 years for activation and 23 percent took more than 2 years; only 16 percent took less than 1 year to begin. The majority of protocols were revised one (35%), two (41%), or three (31%) times. The OEWG's target timeline of 210 days includes: 60 days (down from an average 111 days) for Letter of Intent (LOI) receipt to approval; 60 days (up from 59 days) for approval to protocol submission; and 90 days (reduced from 259 days) for protocol submission to approval. The OEWG recommended the development of a CTEP Action Plan to achieve the target timeline as well as a Collaborative Group/N01/CTEP process for LOI and protocol revisions.

The OEWG suggested that a 90-day timeline be established for Cancer Center investigator-initiated trials, starting with the Protocol Review and Monitoring System (PRMS) review, and a performance benchmark for trial activation set at 180 days. Other recommendations included a Center-specific action plan to achieve the OEWG target timeline and a streamlined university contracting and financial review process.

To achieve process improvements that are applicable across trial categories, the OEWG advocated standardization of tools and templates through the rapid assembly of protocols, enhanced biomarker funding and capabilities by facilitating rapid activation of trials involving critical biomarker studies, and prioritization of Cancer Center trials through the optimal use of resources by reducing the number of protocols in development. Additional improvements to the overall clinical trials program would include enhancing Cancer Center participation in Cooperative Group trials, conducting a strategic review of Cancer Center clinical trials, and enhancing clinical research mentorship and training.

Dr. Doroshow said that the OEWG targets are aggressive but necessary. Commitment to these targets will result in significant progress in the timeliness and effectiveness of clinical trials, but success will not be achieved fully without incremental funding. Termination deadlines, including 24 months for Phase III and 18 months for Phase II, will be implemented in January 2011. In addition, beginning with FY 2011, there should be a routine collection and reporting of timeline performance, incentives for adhering to target timelines, and long-term support for efficiency initiatives. This vision is a coordinated, interactive process for timely development, review, revision, and approval of all NCI-supported clinical trials. OEWG Phase II will address accrual rates and time to trial completion.

Questions and Answers

Dr. Waun Ki Hong, Professor and Head, Division of Cancer Medicine, Department of Thoracic/Head & Neck Medical Oncology, The University of Texas M.D. Anderson Cancer Center, commented on the need for radical cultural changes that encompass a sense of responsibility and accountability for conducting clinical trials, especially as related to experimental therapeutic targets. He encouraged collaboration and team effort and recommended a combination of incentives and enforcement ("carrot and stick") be employed to obtain operational efficiency and scientific accomplishments while building morale, and noted the NCI's role in monitoring performance annually and providing progress reports. Dr. Doroshow agreed and said that until recently, the clinical trials infrastructure and efficiency had never been reviewed, and the NCI can make positive changes.

Dr. Everson asked how the NCAB might assist further in this process. Dr. Doroshow said that it is important for all parties involved to have the Board's review of progress as an extramural body; he expressed the NCI's serious commitment to the 1 January 2011 date and said he would provide progress updates at the Board's request.

Dr. Von Hoff suggested a model in which a committee of investigators from various groups participates in a teleconference each week and hears a sponsor present an agent, which is assigned to a group with 2 weeks to produce a protocol; if the assignment is not completed in that timeframe, the agent is

reassigned. He added that sponsors would be encouraged to bring new agents forth if the work could be under way in 6-8 weeks.

In discussion, members requested a report card composed of absolute data from the NCI-designated Cancer Centers, Cooperative Groups, N01s, and Phase 1 contracts, by site performance and for each cancer, to show which individual groups are reaching or missing the target, particularly for the previous 6 months. Mr. Koch noted that likely a pattern will be revealed showing those who respond quickly and responsibly to the clinical trials requirements. Dr. Chabner also requested that the Board receive a report on how the groups' data would be presented. The data should reveal patterns in adherence (or noncompliance) to timelines, as well as enrollment data to accrual targets, and achievement of milestones. Dr. Coffey suggested that a similar status report should be prepared for the NCI, and he reminded colleagues that the system is composed of a "volunteer army" that should be encouraged throughout the process.

Mr. William H. Goodwin, Jr., Chairman and President, CCA Industries, Inc., suggested that the Board express clearly and formally what its expectations are in this matter. Dr. Gray indicated that Board expectations generally are noted as a standard reporting item expressed by an NCAB member in a particular year. Members requested that Dr. Doroshow give a format to the Board regarding how the data will be presented in the report. Members also expressed a preference for progress reports in 6-month increments; the next report will be scheduled for the December 2010 Board meeting.

Dr. Jennifer A. Pietenpol, Director, Vanderbilt-Ingram Cancer Center, B.F. Byrd, Jr. Professor of Oncology, and Professor of Biochemistry, Vanderbilt University Medical Center, noted Dr. Doroshow's urgency and passion to improve the NCI clinical trials process and applauded the NCI on efforts under way, including Cancer Center Support Grant (CCSG) supplements to Cancer Centers physicians for their efforts in protocol development and patient accrual to trials. Dr. Doroshow acknowledged Dr. Niederhuber's role in establishing these clinical leadership awards.

Motion. A motion was made to accept *Streamlining the Extramural Clinical Trials System: Final Report of the NCI Operational Efficiency Working Group*. The motion was seconded and approved unanimously.

IX. OVERVIEW: NCI TRAINING PROGRAMS: DIVERSITY AND EXTRAMURAL— DRS. SANYA SPRINGFIELD AND JONATHAN S. WIEST

NCI Training Program: Diversity. Dr. Sanya Springfield, Director, Center to Reduce Cancer Health Disparities (CRCHD), provided information about the NCI's Continuing Umbrella of Research Experiences (CURE) program to train more individuals from racial and ethnic minorities and other underrepresented groups in cancer as independent investigators (R01). Dr. Springfield told members that CURE's focus is to emphasize strategic and scientific areas of greatest need, increase the size of the talent pool, and expand and extend the period of training for high school and undergraduate students, predoctoral and postdoctoral researchers, and junior investigators. CURE mechanisms include: supplements to Cancer Centers Program (P30) and Specialized Programs of Research Excellence (SPORE)(P50); NRSA fellowships (F31); supplements to NRSA Institutional Research Training grants (T32); supplements to Cancer Education and Career Development Program (R25); supplements to the Paul Calabresi Clinical Oncology Training Program (K12); and Career and Transition Career Development awards (K01, K08, K22, K23). In addition, diversity supplement funding is provided, with Black and Hispanic students and investigators receiving the largest amount of funding.

The total number of P30 supplements to high school and undergraduate students rose four-fold between FY 2000 and 2009. The number of F32 awards to predoctoral investigators increased six-fold during that time period. Predoctoral research by cancer type includes: breast (38%); prostate (15%); leukemia (10%); and other cancers (37%). In addition, in FY 2009, predoctoral investigators published more than 40 articles in peer-reviewed journals. Dr. Springfield described early stage specialized

supplements and early stage investigator career development (K) awards; the K01 award was the most utilized mechanism, and Black and Hispanic investigators comprised the greatest number of new awardees. Early stage investigator research by cancer type includes: breast (27%); lung (21%); colon/rectum (14%); and other cancers (38%); these investigators published more than 80 articles in peer-reviewed journals in FY 2009.

Unique features of CURE include a Program Director who serves as a career navigator and mentor, provides continual assessment, assists with cultural adaptation, and disseminates a mentoring book and quarterly newsletter. In addition, the program sponsors a professional development workshop and provides mentored peer review. Many CURE trainees work at Cancer Centers, abetted by Minority Institution/Cancer Center Partnership (MI/CCP) training.In addition, 864 minority scholars and faculty were funded by conference grants (R13) to the American Association for Cancer Research (AACR).

Dr. Springfield said that CURE has helped build a pipeline of diverse cancer investigators and mentors. Awardees have produced more than 1,700 scientific publications and received more than 100 competitive grants. In addition, more than 200 committees have provided 18,000 days of review service. Between FY 2005 and 2010, 82 of 334 applications submitted by predoctoral and early stage CURE investigators were funded, for a success rate of 24.6 percent. CURE-supported investigators also have participated as review and advisory members, including mock review participation (64 investigators), NCI *Ad hoc* Review Subcommittee (32), NCI/NIH initial review group (IRG) and Center for Scientific Review (CSR) review committees (28), NCI advisory/review committees (2), and various committees outside the NIH (20). The NCI's investment in CURE training and career development totaled more than $30 M in FY 2009.

CURE is evolving to provide early stimulating exposure to science and careers in cancer research through its K-12 Program as well as its focus on emerging technology to enhance competitiveness, expand technology expertise, and foster successful careers in junior investigators. In addition to R01 awards, 54 R21 applications were submitted, of which 15 (28%) were by CURE junior investigators; 3 of the 6 grants funded (50%) were submitted by CURE-supported researchers. CURE helps build critical mass through training. As part of the cancer health disparities Geographic Management Program (GMaP), CURE and MI/CCP provide training support for basic, clinical, and community-based research that addresses prevention, early detection, diagnosis, treatment, survival, and end-of-life care. Moreover, both domestic and global partnerships are key in integrating research and training and reducing cancer health disparities across the globe. Dr. Springfield concluded by recognizing achievements of past and current CURE investigators and expressed sadness at the passing of Dr. Bobby Rosenfeld, who was a prominent figure in the CURE program.

Cancer Research Training and Career Development Opportunities Supported by the NCI. Dr. Jonathan S. Wiest, Director, Center for Cancer Training (CCT), described the NCI's efforts to train and support the scientific workforce. Dr. Wiest informed members that the CCT is catalyzing the development of a 21st century workforce capable of advancing cancer research through a scientifically integrated approach. The future of cancer research depends on a well-trained workforce in academic and nonacademic natural sciences fields. The NCI Cancer Training Branch's (CTB) support of training and career development grants includes awards for mentored career development and independent career development, as well as transition awards, institutional awards for career development and cancer education, and individual fellowships. The number of CTB awards made between FY 2004 and 2009 mirrors the relatively flat budget experienced during that time period. The CTB's portfolio by activity in FY 2009 included: fellowships (114 awards, $5.7 M); K awards (432 awards, $68 M); R25 awards (85 awards, $28 M); T32 awards (179 awards, $59 M); and other awards (9 awards, $1 M). The success rates for new and competing applications varied by the type of award (K, F32, and T32). The NCI allocates the second largest amount of funds ($163 M) annually to training among the NIH Institutes and Centers (ICs); this totals 3.7 percent of

the total NCI budget. The NCI ranks among the lower half of NIH ICs in its support of training in percentage of total budget devoted to training, career development, and education support.

Dr. Wiest presented information about three CTB extramural award programs. The career development (K) awards program supports mentored career development for early stage investigators, facilitating transition to an independent career. It also provides protected time for newly independent investigators as well as for mid-career or established investigators to serve as mentors across various cancer fields, including: basic science; patient-oriented research; prevention, control, behavior, and population sciences; quantitative science; and stem cell research. The evaluation process incorporates a feasibility study and an outcome evaluation to determine project impact. The National Research Service Awards (NRSA) Program, established by Congress in 1974, provides support for individual and institutional training at the predoctoral and postdoctoral levels. NRSA institutional training grants (T32) have been awarded to institutions throughout the United States; the ratio of postdoctoral to predoctoral students with T32 awards in FY 2009 was two to one. The R25 awards include Cancer Education and Career Development (R25T) and Cancer Education Grants (R25E) programs. The R25T awards, which are institutional grants to develop curricula, are particularly applicable to cancer prevention and control, epidemiology, nutrition, and behavioral and population sciences. The R25E awards support research in cancer education and dissemination of cancer science and health care delivery.

Questions and Answers

Dr. Victoria L. Champion, Associate Dean for Research, Mary Margaret Walther Distinguished Professor of Nursing, Center for Research & Scholarship, Indiana University School of Nursing, encouraged the NCI to disseminate information about supplemental awards through inclusion in communication materials about R25T grants. Dr. Springfield indicated that information about the R25 mechanism is available on the NCI Web site and noted that funding for these supplemental awards is limited.

Mr. Koch asked about the eligibility of foreign citizens for training awards. Dr. Wiest said that mostly that, per Federal rules, most awards require U.S. citizenship or legal permanent residency, with some exceptions such as the K99/R00 program. He agreed that University graduate departments have observed a decrease in the number of foreign national students. Dr. Chabner pointed out that international researchers are supported through NIH's intramural Visiting Fellow Program. Dr. Pietenpol added that RPGs provide informal training to the research workforce without citizenship requirements. In response to a query by Dr. Champion, Dr. Wiest explained that the same process is used in applying for all of the K mechanisms.

Dr. Coffey requested details about how the workforce is analyzed, and he referred to analyses that concluded that highly qualified people, not necessarily the highest degreed people, are needed to process personalized medicine data; more training in the handling of pathological tissues is needed to ensure that pathologists have the samples needed for personalized medicine.

Dr. Hong supported investment in the training of younger scientists from the predoctoral to the R01 level. He asked about the percentage of investigators who receive the T32 award and who also progress to career development awards (K series) and the R01. Dr. Wiest responded that the NCI is working to obtain these figures as part of its planned outcome evaluation.

Dr. Champion supported changes that would increase the percentage of NCI's budget allocated to training, noting that the NCI is sixth from the bottom of 22 Institutes in terms of budget percentage devoted to training. She also recommended that the NCI consider ways to streamline the process of completing the R25 application form.

Dr. Kaur commented that, to attain the IOM goals of increasing the accrual of diverse populations to clinical trials, funding will need to be prioritized to support a more diverse workforce.

A discussion ensued about the NIH and NCI processes to gather specific and cumulative data about the impact of training awards. Drs. Chabner, Pietenpol, and Champion noted that a significant amount of information must be included in application submissions, and the same information often must be repeated in multiple locations on the application form. They strongly encouraged the NCI to compile and maintain this information for training programs, pointing out that such information will facilitate the evaluation of the training program impact. Dr. Springfield said that the diversity program is required to track each of the investigators who enter the training pipeline up to the R01 pool, which is an intensive effort. She added that challenges include that the NCI does not receive self-reporting information about racial and ethnic identity from NIH in general, and that Office of Management and Budget (OMB) guidelines prohibit the NCI from requesting personal data from grantees. Dr. Chabner requested that the NCI address these challenges for mainstream research, if possible. Dr. Springfield responded that the NCI currently is developing a software application tool to assist the Diversity Training Program with its work. Dr. Wiest said that the CCT is preparing full outcomes evaluation of the NCI K grant portfolio with support from NIH OD set-aside funds. Members requested that the NCI provide to the Board a scorecard of NCI-supported cumulative training, gathered on a prospective basis, to identify the optimal sequence of training awards and to track the training of health disparity researchers through a focus on racial factors.

X. CLOSED SESSION—DR. CAROLYN D. RUNOWICZ

This portion of the meeting was closed to the public in accordance with the provisions set forth in Sections 552b(c)(4), 552b(c)(6), Title 5 U.S. code, and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2).

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

The *en bloc* vote for concurrence with the IRG recommendation was affirmed by all serving Board members present. During the closed session of the meeting, a total of 4,882 applications were reviewed requesting support of $1,431,502,503. It was pointed out that this number of grants was the largest ever reported for NCI for one Board meeting for appropriated dollars.

WEDNESDAY, JUNE 23, 2010

XI. REPORT: NCI EXPERIMENTAL THERAPEUTICS (NExT) PROGRAM—DR. JAMES H. DOROSHOW

Dr. Doroshow provided information about the NExT Program, which centralizes NCI's drug development efforts and improves efficiency from target discovery through early stage clinical trials. The NExT pipeline encompasses multiple entry points for all therapeutic development resources and includes investigational drugs and biologics, and investigational imaging agents, as well as academic, biotech, and pharmaceutical projects, and Phase 0, I, and II programs. Dr. Doroshow informed members that the CBC is an important component of the NExT pipeline, helping to increase the flow of early stage therapeutic candidates into the NCI therapeutics pipeline. The CBC consists of Comprehensive Chemical Biology Screening Centers, Specialized Application Centers, and Chemical Diversity Centers, among others, and the participants sign an agreement that governs data transfer, sharing, and ownership. CBC's focus is on academic and small biotechnology development to focus on targets with a higher discovery and market risk.

To access NCI's drug discovery and development resources, extramural scientists propose targets, screens, or molecules for entry into the NExT pipeline by submitting a 5-page online application. Submissions are prioritized by discovery or development specialists and experts from academia and the pharmaceutical industry based on scientific merit, feasibility, the NCI mission, novelty, and clinical need. A Stage Gate evaluation process also is employed to benchmark the progress and priority of projects within the portfolio and provide guidance about the priority utilization of resources. Since the implementation of the NExT application process in September 2009, four quarterly review cycles have occurred, with a total of 174 applications and an approval rate of 19.5 percent for the completed cycles 1 through 3. These statistics indicate a considerable interest in the program. In comparison, the NCI Rapid Access to Intervention Development (RAID) Program, which focuses exclusively on development, received 428 applications in 9.5 years and achieved a 32 percent approval rate.

The NCI's therapeutics platform has the goal of developing treatments for unmet medical needs, providing resources for natural product development and development of high-risk targets, moving discoveries from TCGA into drug discovery, and supporting development of biological agents. Success is measured by the number of IND filings, licensing of novel therapeutics, improved cancer therapeutics success rate, and approved new drug applications.

Dr. Doroshow described several successful NCI-manufactured agents with high potential in cancer therapy and infrastructure. For example, ch14.18, an anti-GD2 monoclonal antibody, demonstrated preclinical activity in neuroblastoma cell lines and xenografts and improved survival for children with high-risk neuroblastoma; another example is the use of inhibitors to target mutant *IDH1* in glioblastoma, a high-risk project that focuses on an unmet cancer treatment need. Other NExT projects include the discovery and optimization of inhibitors of STAT3 activation for the treatment of squamous cell carcinoma of the head and neck, and the inhibition of Mer expression as a target in childhood leukemia. The NExT pipeline is expected to include 20 to 30 projects in the phases of drug discovery and early and late therapeutic development. The program's success depends on a transparent, accountable, inclusive, and unified approach.

Questions and Answers

Dr. Chabner referenced work with the HSP990 compound and asked about measures that the NCI takes to minimize duplication of projects that are pursued by industry. Dr. Doroshow replied that the NCI conducts a formal competitive intelligence analysis from available databases to ascertain all information available about compounds in development. He recognized the importance of not working in areas that already are the domain of industry.

Dr. Chabner commented that Phases I and II appear to be condensing as refinements in patient selection and biomarker definition progress; in time, Phase I studies likely will move directly to clinical trials, providing more information about response rates and benefits that can be expected in selected patient populations. This shift begins to raise questions about the purposes of Phase II and III trials. Dr. Doroshow suggested that the Phase I and II designations be discontinued in favor of "initial target assessment trials" and development of the target during the second phase; he predicted that targets that are defined well enough will preempt the need for large-scale trials. Dr. Chabner raised the issue of refusing effective agents to patients with otherwise incurable diseases because the therapy has not been validated in trial; he said that the NCI should examine and improve the process of making effective drugs available to patients quickly.

Dr. Runowicz related an anecdote of a surgeon who long ago conducted radio-sensitivity studies for cervical cancer, examining samples for every possible biomarker to predict response. Dr. Pietenpol noted that neoadjuvant breast surgeons and SPORE investigators are aware of the role of biomarkers in evaluating the efficacy/response of tumors to novel agents as well as radiation. Dr. Niederhuber added that the

sophistication of interventional radiology allows access to any part of the body. Dr. Chabner commented that circulating tumor cells or circulating DNA also could be used. Dr. Pietenpol said that key elements include determining the best funding mechanisms and obtaining additional biopsies; issues regarding compliance and third party payers present specific challenges.

Dr. Barker complimented Dr. Doroshow on envisioning and championing this effort, despite industry's initial skepticism about the exploratory IND. This will serve as a very valuable tool to use when seeking appropriate biomarkers and likely will enjoy widespread adoption. Dr. Von Hoff asked about the expected size of the program. Dr. Doroshow recognized the high cost of developing new agents; he estimated that NExT will support 20–30 projects, composed of small molecules (approximately $18–20 M) and biologics (approximately $10 M). Dr. Chabner expressed his support for increased funding for this endeavor.

Members expressed interest in hearing updates about NExT, including relevant budget information and progress in supporting specific compound development. Dr. Coffey suggested that presentations include examples of successes and failures of specific compounds that illustrate the program's evolution. Dr. Von Hoff requested that compounds be presented with specific budget information, and he noted that a realistic program budget will allow the Board to better advise on the need for adequate resources; the budget analysis should include an estimate of the funding needed to bring best compounds to fruition.

Dr. Anna Barker, Deputy Director for Advanced Technology and Strategic Partnership, observed that many questions about translational research were raised at recent Congressional hearings; the NCAB could choose to schedule a hearing around translational research and feature NExT or similar programs to provide information on translation to interested parties. Dr. Niederhuber said that therapeutic development may shift to earlier discovery and more difficult targets. He recommended that the Board ensure that the NExT Program not be hampered by responsibilities that it cannot carry out. Dr. Coffey expressed concern that, as a drug development program inside the Federal government, NExT may face significant challenges in addressing policy and bureaucracy issues. Dr. Barker cautioned that the upcoming limiting step in the overall arena is data and noted that TCGA data have reached the NIH's data storage capacity. She suggested that the Board examine the Target Discovery Centers to determine the pipeline effect on analysis and determine if the SPOREs or other programs could assist with this endeavour.

Dr. Chabner suggested that Dr. Doroshow present this information at the NCAB's *Ad hoc* Strategic Vision Working Group meeting in July 2010, including NCI-Frederick's pivotal role in this initiative.

Dr. Pietenpol commented that the presentation could provide an example of the effectiveness of NCI's programs as well as the convergence of work conducted by individual investigators, SPOREs, Cancer Centers, and other groups; some of this work involves basic research with tremendous translational potential.

Dr. Von Hoff recommended that the NCI document and publish this new mode of thinking in a peer-reviewed journal, such as the *New England Journal of Medicine (NEJM)* or *Journal of the American Medical Association* (*JAMA)*. Dr. Hong suggested publishing in *Clinical Cancer Research* (*CCR)*.

Motion. A motion was made regarding the NCI Experimental Therapeutics (NExT) Program to: (1) express the NCAB's consensus that NExT should be considered a high priority for the NCI; (2) request that an annual update about the progress of developing trial compounds, including the nature of the compounds, promising stories, impediments to development, and an aggregated budget estimate based on agent development costs, be provided to the Board; and (3) encourage discussion about both early development strategies and the shift to targeted development with greater FDA involvement. The motion was seconded and approved unanimously.

XII. NCI COMMUNITY CANCER CENTERS PROGRAM (NCCCP): FOLLOW UP— DR. MAUREEN JOHNSON

Dr. Maureen Johnson, Project Officer, NCCCP, NCI, reminded members that the NCCCP is a network of hospital cancer centers that serves as a community-based platform to support basic, clinical, and population-based research initiatives across the cancer care continuum—from prevention, screening, diagnosis, treatment, and survivorship through end-of-life care. Dr. Johnson said that the NCCCP concept rests on seven pillars, three of which she discussed in detail: health care disparities, quality of care, and clinical trials.

Dr. Johnson informed members that the primary challenge for the health care disparities pillar is to ensure that disparity efforts focus on measurable improvements, particularly by improving patient education, patient navigation programs, and community outreach. Metrics include the number and purpose of community partners, the number of cancer patients who are provided navigation, and site collection of race and ethnicity data. Progress in community outreach and navigation during the initial 16 months included 75 percent of sites increasing their number of community partners, 100 percent of sites using patient navigators, 88 percent (up from 44%) of sites establishing community advisory committees, and an increase of 56 percent in both the number of sites that increased community outreach staff and utilized new community resources. The network has developed a disparities vision, work plan, and dashboard with metrics; implemented race/ethnicity tracking following OMB guidelines; and promoted education through cultural awareness Webinars. Dr. Johnson highlighted achievements at the Billings Clinic, Billings, MT, that demonstrated site-specific improvements in disparity issues related to American Indians.

Members were informed that the challenge regarding quality of care is to overcome care coordination issues when working with private practice physicians, and to have data collection methods adhere to guidelines. The goal is to increase the quality of care through increased use of multidisciplinary care conferences (MDCs), evidence-based guidelines, and genetic services and molecular testing. Advances in these areas were measured based on the offering of genetic counseling and molecular testing; adherence to evidence-based guidelines; the number, type and frequency of MDCs; and the year that the conferences began. Improvements in genetic services, molecular testing, and use of evidence-based guidelines included an increase of 81 percent in the number of sites offering genetic counseling, 100 percent (up from 56%) of sites using the Commission on Cancer (COC) eQuIP (Quality Improvement Packets) quality indicators, and an increase of 50 percent of sites with physicians participating in the American Society of Clinical Oncology's (ASCO) Quality Oncology Practice Initiative® (QOPI). On a national level, the network has adopted national quality initiatives, including COC's Rapid Quality Reporting System (RQRS) beta test and QOPI. Sites have increased adherence to evidence-based guidelines at both the hospital and private practice level. They have also established 27 new MDCs and are sharing best practices for network improvement.

NCCCP's goal in clinical trials is to enhance the trial infrastructure to accrue more patients to more trials, increase physician participation, and expand tracking efforts to better understand accrual barriers. Metrics included: patients accrued (total number, and by race and ethnicity); trials opened and early phase trials; types of trials (i.e., prevention, treatment); physicians eligible to enroll patients; and physicians who have accrued patients to clinical trials. To date, the number of NCCCP sites with increases in participating physicians, and in participating nurses and patient navigators has increased by 33 and 50 percent, respectively. In addition, the number of sites tracking individual trials, all trials, and minority accrual across all trials increased from 38 to 63 percent, 31 to 69 percent, and 31 to 100 percent, respectively. Members were informed about the number of clinical trials, by type and phase, which NCCCP sites have conducted since project inception. In total, the sites have accrued 2,606 rural, elderly, and minority patients. Network-level interim accomplishments included increased numbers of participating physicians, available trials, types of trials, and minority accrual. Dr. Johnson described site-specific improvements in clinical trial accrual rates at the NCCCP site, St. Francis Medical Center, Grand Island, NE.

The NCCCP sites also achieved notable results in the areas of survivorship and palliative care, biospecimens, and information technology (IT) including collection of biospecimens for The Cancer Genome Atlas Project and deploying caBIG™ tools. These accomplishments are beyond required deliverables. The program is undergoing an evaluation that includes case studies, patient perspective studies, and economic studies (micro-cost and strategic case); final results will be available in 2011. Interim results of the micro-cost study show that the sites contribute $3.30 for every NCI dollar invested.

Dr. Johnson told members that the NCCCP supports extramural research, providing examples from the H. Lee Moffitt Cancer Center, University of Maryland, and Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) network. These cases illustrated how these NCCCP sites support research, including basic, clinical and health services research. The NCI contributed approximately $80 M of ARRA funds for 2 years of financial support to NCCCP; approximately $40 M was allocated to the pilot sites, supporting 18 projects, and approximately $40 M was committed to adding 14 new community cancer centers to join the network. The network spans the United States, with NCCCP hospitals distributed across the country, serving 23 million people in 22 states. Contributions of the NCCCP network include the treatment of 58,000 new cancer cases per year as a population to support research. The top interim accomplishments to date are investments by the sites in their health care disparities programs, value of the network, and building research capacity.

Questions and Answers

Dr. Niederhuber expressed an urgent need for the NCI to engage directly with the public by bringing quality medical care to communities and to extend such efforts to addressing health disparities; the NCCCP has connected physicians across many disciplines, and the Program's lessons learned have been applied to further progress in other NCI programs. Dr. Niederhuber noted that much remains to be done, and he expressed the hope that the NCCCP will continue its outreach across the United States.

Dr. Karen M. Meneses, Professor and Associate Dean for Research, University of Alabama at Birmingham School of Nursing, expressed support for the program and reflected on the longer time needed to develop research partnerships at the community level than in the laboratory; she encouraged the NCCCP to examine multiple evaluation methods to measure results. She also noted the unique opportunity that the NCCCP offers for interaction between academic investigators and communities and encouraged the NCI to capitalize on the Program's success stories. Dr. Champion recommended that the NCCCP centers serve as laboratories for population-based and behavioral research in addition to biology. She also requested and received clarification about data concerning clinical trials by type.

Drs. Chabner and Runowicz requested that future presentations provide data as absolute numbers, not as percentages that are difficult to interpret. Dr. Chabner remarked that the NCCCP is an interesting system, and he recognized the difficulty in obtaining measurements in a climate of many changing parameters. He encouraged Program staff to work with CTEP on how best to present clinical trial data to help the Board better understand the Program's impact. Dr. Chabner recommended a stronger focus on disparities and pointed to the low minority accrual rate. Dr. Johnson confirmed that all sites now are required to track minorities and adhere to OMB guidelines.

Dr. Barker said that the NCCCP is making progress in the biospecimen realm. During prospective collection efforts, a learning curve will be implemented at the community centers, which are the source of most biospecimens. It is possible that designated Cancer Centers will develop an appropriate network for high-quality biospecimens. Dr. Barker noted the strong interest in this subject in Congress, and said that, similar to Congressional interest in organ transplants, biospecimens are perceived as having high financial impact and providing a basis for personalized medicine; she said that resolution of extant issues could preempt the need for biospecimen regulations.

Dr. Lopez recommended that future sites be selected based on strong minority representation in the location. Dr. Niederhuber agreed and noted that sites have been selected thus far on a competitive basis.

XIII. NCI EFFORTS IN HEALTHCARE INFORMATICS—DR. KEN BUETOW

Dr. Ken Buetow, Director, Center for Bioinformatics and Information Technology, provided an update report on caBIG®. caBIG® is a virtual network of interconnected data, individuals, and organizations that redefines how research is conducted, care is provided, and patients/participants interact with the biomedical research enterprise. Dr. Buetow told members that the network represents a rapidly expanding virtual community with more than 2,300 participants from more than 700 institutions and provides connectivity to more than 40 applications and 40 nodes, which are connected to the national grid via caGrid. caBIG® also links to 1.19 million biospecimens and to more than 3.71 million medical images and 25,000 microarray experiments. In 2009, 30 peer-reviewed scientific publications featured or were enabled by caBIG® tools and technology. Currently, 16 licensed support services providers and 15 countries use caBIG® tools and technology.

caBIG® supports a variety of usage patterns. For example, the University of Arkansas uses the network in a hybrid function with interfaces to vendor applications for managing institutional clinical research. It also provides integrated access to multidimensional data, including TCGA and the Cancer Molecular Analysis Portal, which enables users to access, search, visualize, and integrate genomic data with corresponding clinical information and facilitates access to data from other research studies. These capabilities support researchers with the volume of data resulting from molecular and pathway analyses, such as TCGA glioblastoma results and the screening of HER2 breast cancer patients for treatment based on phenotype signature subgroups.

Dr. Buetow said that a new caBIG® strategy is to leverage the Nation's health IT investment for applications in research. Funds totaling $46 B have been allocated to incentivize the "meaningful use" of electronic health records (EHRs). Research requirements include: oncology-specific EHRs as a source of clinical information, annotated biospecimens, images, and molecular data; and a data-sharing infrastructure to capture, aggregate, analyze, and appropriately share large amounts of information from millions of patient-physician encounters. An additional requirement is the ability to prospectively identify subgroups of patients and collaborate across organizations to test research hypotheses. The NCI currently collaborates with ASCO, caBIG®, NCCCP, and numerous proprietary and open source EHR vendors.

The extended EHR is meant to amend, not reinvent, the traditional EHR to support clinical oncology care. Requirements for the EHR include information collection, decision support, and reporting needs of the oncologist providing patient-focused care in a clinical setting; this involves generation and transmission of a treatment plan and summary as well as support of oncology-specific documentation and EHR functionality. This leverages the efforts of caBIG® because the data collection from patients enrolled in clinical trials is similar to capturing information from patients during clinical encounters. Dr. Buetow said that a framework based on an "ultra-light" oncology EHR could serve as an on-ramp to electronic health for community practices. caBIG® efforts in this arena include collaboration with the NCCCP Outcomes Database Project, which enables NCCCP sites to aggregate and analyze standard clinical encounter data that can be used to support decision-making for physicians and administrators, as well as the rapid-learning health care system.

Electronic health information is one of many information sources within the biomedical community; others include clinical trials, molecular profiling, exposure information, biospecimens, and adverse events. Through caBIG®, researchers can query or submit data from these sources, providing a loop of information that extends from EHRs through research and back to clinical care. Dr. Buetow illustrated how information can be used to analyze treatments and predict the change in mortality for a subset of data

through examples of treatment outcomes and mortality comparison for prostate cancer. The caBIG® information infrastructure provides researchers unprecedented access to extensive resources.

Integrating research and care currently is under way in the ISPY-2 Trial (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis), a national Phase II biomarker study being conducted by Dr. Laura Esserman, Principal Investigator, University of California, San Francisco (UCSF). The study design is unique for its simultaneous evaluation of multiple interventions using a rapid-learning system. Feedback concerning successful and unsuccessful methodology is provided continuously in near real-time during the course of the study, thus achieving a synergistic outcome.

In conclusion, Dr. Buetow stated that caBIG® connects the cancer community nationally and internationally to enable a wide spectrum of clinical discovery and research activities. It leverages new opportunities in health IT to support increasingly complex research studies, and its national infrastructure bridges both research and health care.

Questions and Answers

Dr. Coffey commented on the importance of IT initiatives in facilitating cancer therapy and requested a future presentation on how the NCI is addressing IT limitations in dealing with an increasing amount of data about numerous molecular pathways and phenotype subgroups that may serve as biomarkers for targeting agents. Dr. Runowicz observed that the NCI, NCAB, ASCO, AACR, and other leaders in the National Cancer Program need to stand behind/support the oncology EHR, given that incentives will support primary care physicians, not oncologists. Dr. Buetow answered that reimbursements can be directed to any qualifying EHR that meets the "meaningful use" criteria. Unfortunately, no criteria exist for the oncology EHR. It will be important for NCAB and other boards to articulate the importance of specialty care.

In response to a query by Dr. Runowicz's about Dr. Barker's testimony to Congress on oncology IT issues, Dr. Barker explained that the caBIG® enterprise is not well connected to incentive prerequisites. Patient care and research have been particularly hampered by the omission of linking important parameters such as biospecimen annotations to clinical records. She informed members that Congress has expressed criticism about this failure and the noncompliance with requirements.

Dr. Hong said that the NCI's development of health care informatics and biospecimen collection are prerequisites to attaining personalized medicine. He underscored the importance of communicating and connecting with the cancer community and recommended publication of a white paper and articles in peer-reviewed, major scientific journals. Dr. Buetow highlighted the deep complexity of the endeavor, noted the NCI's collaborative efforts with the HHS' Office of the National Coordinator (ONC), and invited member comments on IT implementation efforts. Dr. Niederhuber suggested that the ONC focus its efforts first on oncology in one geographical area rather than trying to improve the entire field of primary care simultaneously. Dr. Coffey said that the IT endeavor should not allow challenges to decelerate progress in health care informatics.

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

NCAB Subcommittee on Clinical Investigations. Dr. Hong, Chair, Clinical Investigations Subcommittee, informed members that the Subcommittee discussed changing the NCI's clinical trials to meet the needs of the 21st century. Dr. Hong said that Drs. Jeffrey Abrams and Margaret Mooney provided excellent overviews to the Subcommittee on the topic, followed by productive discussions about: (1) high priority trials; (2) rapid protocol creation; (3) CIRB; (4) central patient enrollment; and (5) standard tools for conduct of trials.

In the area of high-priority trials, scientific steering committees have been formed to prioritize large-scale national clinical trials. The steering committees ensure well-informed evaluation of strategic directions; approximately 98 trial concepts have been evaluated thus far, with an approval rate of 56 to 60 percent. The creation of rapid protocols is based on the OEWG's recommendation to reduce the time for activation of Cooperative Group and Cancer Center trials targeting a 50 percent reduction in protocol activation time. The target for all three steps is 300 days, and if a Phase 3 trial is not open to patient enrollment within 2 years from initial submission for review, it will not go forward. A total of 42 of 65 cancer centers have joined the CIRB, which oversees all adult Phase 3 and pediatric Phase 2 and Phase 3 trials conducted by the NCI Cooperative Groups. The HHS Office for Human Research Protections (OHRP) expressed its agreement with FDA's position on the benefits of relying on a single CIRB for multicenter research. CIRB affiliation also has been associated with time and cost savings. The timeline from CIRB receipt to approval has decreased from 157 days in 2007 to 36 days in 2009–2010. Improvements in central patient enrollment include that the CTSU has centralized administrative and regulatory functions for NCI clinical trials. More than 45,000 patients were enrolled via CTSU since 2002. Regarding the standard tools developed for trial conduct, a common, comprehensive Clinical Trials Data Management System will begin implementation by the end of 2010. The system includes: standards for data collection using remote data capture; a completed set of FDA-grade electronic case report forms using common data elements; and implementation of a common electronic protocol authoring tool. Dr. Hong said that the Subcommittee requested that the NCAB continue to receive updates from the CTEP about progress made in these areas.

Dr. Chabner noted that several important points were raised during the Subcommittee's discussion, including that this effort should carefully monitor consolidation efforts, particularly in reference to adult oncology groups. The NCI should help simplify the review process by eliminating its review of non-IND trials. In addition, the number of trials should be reduced, particularly of those that have poor accrual rates; a system is needed to identify in a prospective way those trials that will not reach desired accrual rates. Funding increases should be dependent on demonstrating a willingness to change the system and implement the changes. Dr. Runowicz added that because the budget has been flat for an extended time period, and when taking the cost of living into consideration, the per-patient reimbursement is a detriment. One way to increase funding for promising trials is to decrease the funding of poorly accruing trials in the system. Dr. Kaur said that the Subcommittee would like to receive semi-annual updates to evaluate the progress made.

Motion. A motion was made to accept the summary report of the 21 June 2010 Subcommittee on Clinical Investigations meeting. The motion was seconded and approved unanimously pending the inclusion of discussion points and typographical corrections in the summary.

NCAB *Ad hoc* Subcommittee on Experimental Therapeutics. Dr. Von Hoff, Chair, *Ad hoc* Subcommittee on Experimental Therapeutics, informed the Board that the Subcommittee heard a presentation by Dr. Joe Tomaszewski, Deputy Director, DCTD, about the history of the NCI's therapeutics development program. Dr. Von Hoff said that many of the NCI's individual drug development activities are now merged into the NExT Program, including the RAID Program. The most recent evaluation of the RAID Program showed impressive results: 428 applications, 137 approved, 115 complete, 50 INDs filed, and 41 agents licensed. Other drug development programs that have been merged into the NExT program include: the Drug Development Group, which managed NCI-held INDs; Development of Clinical Imaging Drugs and Enhancers (DCIDE), which was an imaging program for molecular and imaging probes; PD-Biomarkers Program, which validates DNA damaging markers; the Phase 0 trials program, with the exploratory INDs and HARP inhibitors; and the Joint Development Committee (JDC), which involves NCI-academic partnerships and accounts for 19 compounds.

Dr. Von Hoff said that the Subcommittee addressed several questions raised by NCI staff. Regarding new directions that the NCI should pursue, the Subcommittee recommended simplifying the NCI drug development system, which is being done through the NExT program. Dr. Von Hoff noted that the

Board made an important motion earlier in the meeting regarding NExT and certified the motion about this, particularly to receive regular reports about the number of compounds under development and about the budget. The Subcommittee suggested several topics for future efforts, including further information on mutations and total sequencing. Another suggestion was to examine defined models (e.g., genetically engineered models) because of concerns about the NCI 60 as well as PI3 kinase, PTEN deleted, AKT elevated, and other engineered isogenic lines. The Subcommittee agreed that the progress made is solid, but encouraged publishing to raise the cancer community's awareness of these advances. The strongest measure of success is the number of INDs; other metrics could include the time to a go/no-go decision and the "success ratio", that is, the ratio of approved agents over the number of evaluated therapeutics.

Motion. A motion was made to accept the summary report of the 22 June 2010 *Ad hoc* Subcommittee on Experimental Therapeutics meeting. The motion was seconded and approved unanimously with typographical corrections in the summary.

XV. 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 154th regular meeting of the NCAB was adjourned at 11:39 a.m. on Wednesday, 23 June 2010.

_____ _____

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

_____ _____

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