DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
143rd NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
September 17-18, 2007

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

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The National Cancer Advisory Board (NCAB) convened for its 143rd regular meeting on 17-18 September 2007, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Monday, 17 September 2007, from 8:30 a.m. to 4:27 p.m. and closed to the public from 4:27 p.m. to 5:30 p.m. The meeting was open to the public on Tuesday, 18 September 2007 from 8:00 a.m. until adjournment at 11:05 a.m. NCAB Chair Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, Farmington, CT, presided during both the open and closed sessions.

NCAB Members
Dr. Carolyn D. Runowicz (Chair)
Dr. Anthony Atala
Dr. Bruce A. Chabner
Dr. Moon S. Chen, Jr.
Dr. Donald S. Coffey
Dr. Kenneth H. Cowan
Dr. Jean B. deKernion (absent)
Dr. Lloyd K. Everson
Dr. Judah M. Folkman
Ms. Kathryn E. Giusti
Mr. Robert A. Ingram (absent)
Mr. David H. Koch (absent)
Dr. Diana M. Lopez
Dr. Karen M. Meneses
Dr. Franklyn G. Prendergast (absent)
Ms. Lydia G. Ryan (absent)
Dr. Daniel D. Von Hoff (absent)

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

Alternate *Ex Officio* NCAB Members
Dr. Irma E. Arispe, OSTP (absent)
Dr. Michael A. Babich, CPSC (absent)
Dr. Allen Dearry, NIEHS (absent)
Dr. Raynard S. Kington, NIH (absent)
Dr. Peter T. Kirchner, DOE
Dr. Richard Pazdur, FDA
Dr. John F. Potter, DOD
Dr. R. Julian Preston, EPA (absent)
Dr. Dori B. Reissman, NIOSH (absent)
Dr. Donald J. Wright, DOL

Members, Executive Committee, National Cancer Institute, NIH

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

Liaison Representatives

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

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I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF 14-15 JUNE 2007 MINUTES—DR. CAROLYN D. RUNOWICZ

Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, Farmington, CT, called to order the 143rd NCAB meeting. She welcomed members of the Board, the President's Cancer Panel (PCP), *ex officio* members of the Board, liaison representatives, staff, and guests. Members of the public were welcomed and invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), National Cancer Institute (NCI), in writing and within 10 days, any comments regarding items discussed during the meeting. Dr. Runowicz reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Motion. A motion was made to approve the minutes of the 14-15 June 2007 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 2008. She said that the September 2008 dates would be changed, however, and that members would be informed of the new dates once they were determined.

III. DIRECTOR'S REPORT—DR. JOHN NIEDERHUBER

Dr. John Niederhuber, Director, NCI, began his report by welcoming NCAB members, as well as Executive Committee (EC) members and staff. He then introduced to the Board Mr. Lawrence J. Ray, who was recently appointed as Deputy Director for Management and Executive Officer of the NCI.

Year-End Budget Summary. Dr. Niederhuber said that the research project grants (RPGs) have been funded at the 15th percentile plus extensive exceptions, which equates to an approximately 20 percent success rate. *R01 grants have been funded at the 21st percentile extended payline plus exceptions; the number of grants funded will exceed the 205 grants that were projected. Type 5 grants were reduced by 2.9 percent on average. The NCI likely will fund 1,314 competing RPGs in fiscal year (FY) 2007, meeting the NIH-recommended target. In addition, this year the NCI funded two new Cancer Centers: Baylor College of Medicine and Stanford University.

New Investigator Awards and Challenges to the NCI. Dr. Niederhuber stated that the NCI will be exceeding the targeted number of new investigator awards that the NIH established for the NCI. He explained that the proposed President's Budget (PB) for FY 2008 is slightly under $4.8 B for the NCI and reflects a decrease of approximately $9 M from the FY 2007 level. The House and Senate appropriations are for $4.87 B and $4.91 B, respectively. It is anticipated that the NCI's FY 2008 budget will be somewhere between these numbers. Dr. Niederhuber pointed out that the appropriation bills contain specific language regarding an obligation to increase the number of funded grants, the lift of a 2-year freeze on the average cost of a new grant, and the need for increased efforts in training the next generation. In addition, the House allocates $495 M (i.e., an increase of $12 M) to the Common Fund, and the Senate allocates $531 M (an increase of $48 M) to the Common Fund. NCI planning currently involves a 3 percent decrease in the Divisions, Centers, and Office of the Director (OD) budgets.

Dr. Niederhuber described several challenges facing the NCI. These include the pressure on investigators to overcome inflation and the mandated cuts to each award, the poor rate of success by *A0

applicants (i.e., need for required mentoring program), and concerns about peer review. Other issues are the preparation of the NCI, NIH, and the university research community for a transformation in the conduct of science and the need to attract the best students to careers in bioscience.

Genome-Wide Association Studies (GWAS). The NCI has continued to lead in the GWAS program. The program focuses on the ability to use a single nucleotide polymorphism (SNP) approach to finding changes in the genome (i.e., the germ line genes, which are what a person comes into the world with). This is an exciting approach trying to develop a pattern of risk that individuals have for certain specific diseases, including cancer. The GWAS program focuses on a variety of cancers, including primary scans involving breast, prostate, pancreatic, lung, and bladder cancers. In addition, work in replication involves colorectal, kidney, non-Hodgkin's lymphoma (NHL), and ovarian cancers.

Dr. Niederhuber presented details about a GWAS strategy to identify genetic markers for prostate and breast cancer, which includes an initial study, two followup studies, and fine mapping of genotype, haplotype, and sequencing to identify a small number of loci that seem to be the pattern that predicts risk. The Cancer Genetic Markers of Susceptibility (CGEMS) prostate cancer study is another replication study that shows how the extensive amount of power can be gained from these studies. Much work has been completed in prostate, breast, and colon, but there are still unknown areas, including gene regulatory areas and risk prediction.

The Therapeutically Applicable Research to Generate Effective Treatments (TARGET) Initiative also is using current genomic technologies to develop molecular targets in pediatric cancer. Two pilot projects are acute lymphoblastic leukemia (ALL) (Children's Oncology Group [COG]) and neuroblastoma and include the coordinated analysis of clinical data, somatic characterization, and sequence analysis. NCI's Board of Scientific Advisors (BSA) follows the initiative's work through its Oversight Subcommittee.

The Cancer Genome Atlas (TCGA) Project also is working in the genome arena. There is an ongoing pilot project co-sponsored by the NCI and National Human Genome Research Institute (NHGRI) addressing brain, lung, and ovarian cancers. This work involves the Human Cancer Biospecimen Core Resource, Genome Sequencing Centers, and Cancer Genome Characterization Centers to perform data management, bioinformatics, and computational analysis.

NCI's Drug Discovery Initiative. Dr. Niederhuber told members that Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), would be presenting information about the NCI's efforts in drug discovery, including the Chemistry Biological Consortium, work in Phase 0 trials, and updates on the implementation strategies of the Translational Research Working Group (TRWG) and the Clinical Trials Working Group (CTWG). Dr. Niederhuber said that the NCI intends to reorganize and strengthen the drug discovery platform within 6 to 8 years, and these efforts are important parts in that plan. The NCI has a key role in the development of public-private partnerships and can serve as an honest broker between government, academia, and the private sector.

The NCI is building this platform internally by recruiting needed talent and externally by creating relationships through the Clinical Research Center or Clinical Laboratory, which is a new clinical facility. The laboratory is being made more available to the extramural community. Dr. Niederhuber referred in more detail to NCI's support of Phase 0 trials in oncologic drug development and to the Chemistry Biological Consortium's work with NCI's Experimental Therapeutic Center, Specialized Programs of Research Excellence (SPORE) program, Cancer Centers program, and the Rapid Access to Intervention Development (RAID) program as further examples of strengthening the platform. The challenge with the SPORE program, for instance, is to take a large amount of genomic information and translate it into cell

biology, function, changes in protein structure, and protein-protein interaction, and understand how that changes the individual and causes disease.

The Clinical Research Center and the NCI. The Clinical Research Center is an inpatient ambulatory facility at the NIH Campus. Approximately 40 percent of its activity involves cancer, and the NCI supports its pathology, radiation therapy, and surgery. Because of the NCI's interest in imaging and the importance of imaging to the processes of drug discovery, new therapeutic molecules, and translation, the NCI has proposed to establish a Center of Excellence in Imaging within the Clinical Research Center, under the direction of Dr. Steve Katz, which will be devoted primarily to cancer. A mini-retreat was held in July 2007 with Institute and Center (IC) Directors to discuss the science that is hoped to occur in the imaging center during the next decade. Long-term issues that the imaging center might be able to assist with include the need to recruit and retain young researchers who would be able to conduct their research in a timely fashion (i.e., 2 or 3 months instead of 9 months) from idea to first patient. Short-term issues for the imaging center include work in inflammation, immunology, and autoimmunity as a trans-NIH effort and for cancer, Clinical and Translational Science Awards structure, extramural collaborations, and increasing the number of rare or difficult diseases handled by the Clinical Research Center. Another topic is the identification of Manhattan-like projects that can be trans-NIH in activity, such as imaging.

Dr. Niederhuber concluded by reiterating NCI's commitment to serve as a connecting platform among the various stakeholders to facilitate cancer research: the pharmacology and biotechnology industries, universities, NCI's centers program (including the Community Clinical Oncology Program [CCOP]), and others. He noted that the NCI will serve as an anchor facility with the community in the development of an Advanced Technology Research Park, which the Department of Health and Human Services (DHHS) recently approved, and it will continue the NCI Community Cancer Centers Program (NCCCP). Dr. Niederhuber also expressed deep sadness at the death of Dr. Martin D. Abeloff, former Chief Oncologist and Director of the Johns Hopkins Kimmel Cancer Center, and an important member of the NCI and NIH community.

Questions and Answers

Ms. Kathryn Giusti, CEO and Founder, Multiple Myeloma Research Foundation, Inc., applauded NCI's focus on translational work, including its efforts to decrease drug development time and increase the involvement of Cancer Centers and SPOREs. She also commended the role of the PCP and the Lance Armstrong Foundation, and Mr. Lance Armstrong specifically, for their public role and consistent communication strategy in addressing issues of access, insurance coverage, and the need for new researchers. Dr. Niederhuber agreed and said that he recently had the privilege sitting on a panel held during the PCP's meeting in Atlanta, GA, and encouraged members to attend PCP sessions. He also said that Dr. LaSalle Leffall, Jr., Chair, President's Cancer Panel and Charles R. Drew Professor of Surgery, Howard University College of Medicine, has agreed to continue serving as the Chair of the PCP.

Dr. Bruce Chabner, Clinical Director, Massachusetts General Hospital, said that he thought that Dr. Abeloff would be proud of the values that Dr. Niederhuber stated in his report because they reflect his overriding concern of bringing science to patients. He commended Dr. Niederhuber for recognizing the importance of keeping investigators, particularly young investigators, in this field; the significance of raising the payline cannot be overemphasized in persuading young researchers to remain in academic medicine. He added that individual creativity is the basis of progress in cancer research. Dr. Runowicz noted Dr. Niederhuber's emphasis on mentoring as well.

Dr. Runowicz asked how the transformation of the SPORES program from silos to matrix is envisioned. Dr. Niederhuber said that there is no easy answer, but that the SPOREs and the Cancer

Centers will play a key role in translating the huge amount of information into how that impacts on cell signaling pathways, how a network changes, how protein structure changes, and the development of disease. There are commonalities, for instance, that will be informative and important in terms of prevention.

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, suggested that the NCI could analyze various successes, such as Temperance 2 with prostate cancer, and understand clearly how such breakthroughs occurred; the American Society of Clinical Oncology (ASCO) and American Association for Cancer Research (AACR) might be in positions to assist with this endeavor. Dr. Niederhuber said that the NCI's interest in this idea is one of the reasons that the Institute is considering how to bring experts in physical and mathematical sciences into its work.

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

Dr. Leffall opened his presentation by thanking Ms. Giusti for commending, during the discussion of the Director's Report, the efforts of Mr. Armstrong as a member of the PCP. Dr. Leffall thanked Dr. Niederhuber for attending the most recent meeting of the Panel, and expressed his sadness about the loss of Dr. Martin Abeloff as a friend and contributor to the cancer field.

Dr. Leffall described the PCP's 2006–2007 meeting series, *Promoting Healthy Lifestyles To Reduce the Risk of Cancer*. The series covered two topics: 1) obesity, nutrition, and physical activity; and 2) tobacco and environmental tobacco smoke. Discussions on obesity were held in Minneapolis, MN, on September 11, 2006, and Portland, OR, on December 5, 2006. Discussions on tobacco were held in Lexington, KY, on October 23, 2006, and Jackson, MS, on February 12, 2007. Personal, policy, and program recommendations and research needs for reducing cancer risk were identified during these discussions.

Panel recommendations for obesity, diet, and physical activity include: reinstating physical education programs and daily recess periods within school systems; designing new communities and retrofitting existing communities to provide opportunities for physical activity and to increase personal and family fitness; improving access to affordable, healthy foods, particularly in schools and low-income neighborhoods; regulating food advertisements targeting children, especially ads for high-fat, high-sugar, and high-caloric foods; providing health care coverage for nutrition counseling and fitness programs; and seeking opportunities to increase personal and family fitness and health. The Panel noted that several of these recommendations were relatively easy to implement, such as including sidewalks in communities to encourage more walking, running, biking, and skating. Implementation of these recommendations would help individuals and families make healthier lifestyle decisions.

Future research needs include assessing the influence of obesity, physical activity, and diet on specific cancers. There is evidence of increased risk for breast, colorectal, and prostate cancer in patients who are obese. Although a causal relationship has not been established, the public needs to be made aware of the associations between obesity and cancer risk. The NCI also should investigate the role of energy balance in cancer survivorship and prognosis. Considering the increasing numbers of cancer survivors and the role that obesity may play in the development of a new diagnosis (or decreased quality of life), the NCI needs to vigorously pursue research on the role of energy balance in this population. In addition, research needs to focus on developing improved tools to measure physical activity and collect data on diet and obesity.

Panel recommendations on tobacco use and secondhand smoke include but are not limited to: ratifying and fully implementing the Framework Convention for Tobacco Control; authorizing the Food and Drug Administration (FDA) to strictly regulate tobacco products and product marketing; increasing the Federal excise tax on tobacco products; adopting smoke-free ordinances in all public spaces; including coverage of tobacco cessation services in all health benefit packages; and quitting smoking and the use of smokeless tobacco products.

The Panel developed three recommendations for reducing smoking and secondhand smoke that could be facilitated by the NCAB: 1) reallocate the NCI, Centers for Disease Control and Prevention (CDC), and other Federal resources to better mirror the tobacco-related disease burden; 2) add the conduct of meaningful tobacco-related activities to the evaluation criteria for the NCI cancer centers; and 3) prohibit recipients of NCI grants and contracts from accepting money from tobacco companies.

Future research needs in this area include assessing the impact of tobacco marketing strategies specific to vulnerable populations; improving methods to assess the type, amount, and toxicity of elements in tobacco and tobacco smoke; and developing tools for quantifying individual smokers' risk of lung cancer based on genetic and environmental variables.

The first overarching recommendation from the 2006–2007 meeting series states that elected officials, policymakers, and institutions have a moral obligation to protect public health and must assert the political will to change policies. Second, the health care community must coordinate and integrate education and prevention messages related to cancer and other diseases. Third, individuals must assume personal responsibility for learning about cancer risk and adopting a healthy lifestyle. The Panel is emphasizing the importance of patient-centered involvement in research, detection, and treatment.

Dr. Leffall next presented discussion questions for the 2007–2008 meeting series of the President's Cancer Panel entitled *Strategies for Maximizing the Nation's Investment in Cancer*. This series of meetings will focus on strategies uncovered through group discussions with experts in the cancer field. The first meeting took place in Atlanta, GA, on September 10, and future meetings will be held in San Diego, CA, on October 22; San Juan, PR, on December 3; and New Orleans, LA, on January 28, 2008.

Dr. Leffall concluded his presentation with an overview of issues that were raised at the Atlanta, GA, meeting, which includes hurdles to cancer research such as restrictive regulatory activities, intellectual property issues, low numbers of participants in clinical trials, and lack of—or insufficient access to—adequate health care.

Questions and Answers

Ms. Giusti asked whether representatives from industry and foundations attended the Atlanta, GA, meeting as this would seem to have been an ideal forum to integrate work that the patient groups are doing with industry and the NIH. Dr. Leffall said that a list of attendees can be made available at later sessions. The meeting emphasized that health care is the responsibility of not just government, but of everyone, including private organizations, pharmaceutical companies, and insurance companies.

V. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), expressed appreciation to those who responded to her survey and indicated that she would focus her presentation on more selective legislation, in response to survey feedback. She opened the discussion

with an introduction of items that could have a direct impact on the NCI and those that would likely see significant activity in Congress: the FY 2008 Appropriations bill, the Small Business Act, and the Tobacco bill.

The House has passed all 12 of its bills for FY 2008 appropriations, but the Senate has only passed 4 of the 12. Ms. Erickson outlined the proposed appropriations of the Labor, HHS, and Education bill. House appropriations, estimated at $4.87 B to the NCI, passed in July. The Senate bill, which proposes $4.91 B for the NCI, was passed by the appropriations committee in June, but the full Senate has yet to act on it.

The current administration has issued a formal veto threat to the Labor HHS bill, most likely due to what the administration has identified as spending in excess of the President's recommended levels. There is speculation, however, that the Labor HHS bill could be enacted if it is combined with one or more appropriations bills. For example, if it is combined with the defense bill or combined with several other bills into an omnibus bill, it will be less likely to be vetoed. Chairman Dave Obey (D-WI), Chairman of the House Appropriations Committee, has stated publicly that he feels a continuing resolution is likely. The first continuing resolution could be in effect for a minimum of 6 weeks, it would be enacted prior to September 30, and last until as late as December 2007.

The Small Business Act Amendment was introduced in August 2006 by Senator Evan Bayh (D-IN). The Amendment would incrementally increase the set-aside for the Small Business Innovation Research (SBIR) and Small Business Technology Transfer Research (STTR) programs from 2008 to 2013. Both the Senate and the House have held discussions about the Amendment, but as yet there is no bill in the House. The Senate and House hearings were attended by the NIH leader of the SBIR Program; Department of Energy; National Aeronautics and Space Administration; and National Science Foundation. The NIH is not in favor of increasing the set-aside because it would decrease the flexibility of the Institutes to set their priorities and allocate their resources.

The key provision of the Tobacco Bill, formerly referred to as the Family Smoking Prevention and Tobacco Control Act, authorizes the FDA to regulate the specific sale and manufacture of tobacco products by: restricting tobacco advertising and sales to youth; requiring manufacturers to supply information on ingredients and the construction of products; regulating modified risk products; requiring premarket approval for new tobacco products; establishing a tobacco products scientific advisory committee; and assessing user fees based on the costs to the FDA.

There are companion bills in the House and Senate—in February, 2006, Senator Edward Kennedy (D-MA) introduced the Senate bill, and Representative Henry Waxman (D-CA) introduced the House bill. The legislation has been endorsed by more than 70 health organizations. The Health Committee in the Senate held several sessions in July and reported on the bills on August 1. Opposition to the bill appears to be centered around the seemingly implicit approval of tobacco smoking if the FDA becomes authorized to regulate it.

Ms. Erickson ended her presentation by directing participants to the new Web site for the OGCR (http://legislative.cancer.gov//), which contains legislative updates, hearing testimonies of the NCI representatives since 1997, and legislative histories. A hardcopy of the Activities of the 110th Congress was included in participants' program books.

Questions and Answers

Several NCAB members indicated their interest in the tobacco bill and regulation by FDA. Dr. Chabner asked about industry's position on the bill because some tobacco companies seem to be supporting it, whereas others are not. Ms. Erickson referred the question to Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences (DCCPS), who explained that the main industry supporter of the bill is Philip Morris, the company which currently holds the dominant share of the market. One theory about industry support of the bill is that restrictions in marketing and advertising may prevent changes in the industry and help dominant companies to maintain a competitive edge over small companies.

Dr. Chabner noted that provisions of the bill seemed relatively weak and that the FDA should have the power to enforce severe limitations on where people could smoke and what people could smoke. Dr. Croyle pointed out the issue of considering what is appropriate within FDA's authority as a Federal agency versus that of the Federal Trade Commission. One of the challenges of the tobacco bill encompasses FDA's role and whether or not specific elements of the bill fall within FDA's charter.

Dr. Runowicz cited the American Cancer Society's (ACS) support of the current bill by reading an excerpt from its Cancer Action Network list of priorities. Dr. Croyle added that currently there is an element in the State Children's Health Insurance Program (SCHIP) bill on Capitol Hill to increase the excise tax on cigarettes as a way to fund SCHIP. Dr. Runowicz asked for an update on the Feinstein-Brownback bill, and Ms. Erickson stated that the Feinstein-Brownback bill has been referred to the Senate Health, Education, Labor, and Pensions (HELP) Committee.

VI. ANNUAL REPORT: AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO)— DR. NANCY E. DAVIDSON

Dr. Nancy E. Davidson, President, ASCO, presented an overview of ASCO, its mission, activities, and accomplishments over the past year. ASCO's primary mission is to improve cancer care and prevention by advancing education and training of cancer professionals, fostering communication among the cancer community, advocating for sound policy, and supporting oncology professionals who practice across all settings. Membership is split evenly between medical oncology/hematology and other medical specialties in private practice and academic settings, and approximately 30 percent of members practice in a country outside the United States. This diversity is what gives ASCO its strength to meet the challenges of tight budgets, regulatory burdens, demand for accountability, and a growing concern over the costs of cancer care. Dr. Davidson gave examples of existing relationships that could be built upon to meet these challenges. Many ASCO members serve on key advisory committees of the NCI, including the CTWG, TRWG, NCAB, and BSA, and several staff members of the NCI serve on the Board and other committees of ASCO. The NCI and ASCO share common goals that include: 1) bridging the "bench to bedside" gap; 2) assuring the finest care to every patient; 3) fostering clinical and translational research; and 4) building the next generation in oncology.

Recent collaborative efforts among other agencies and groups that share these goals have focused on identifying surrogate endpoints that could be used for drug development and developing quality-based performance initiatives. Related activities—sponsored by the FDA, American Society of Hematology (ASH), AACR, European Organization for Research and Treatment of Cancer (EORTC), TRWG, CTWG, and the SPORE program—have included think tanks on pursuing disease- and biology-specific research, alternative trial design meetings, biomarker development symposiums, and clinical trials workshops. Continued partnerships and collaborative activities among the cancer community will help reach the common goals. During the past year, ASCO established a new quality care committee and

clinical practice and treatment guidelines. The Quality Oncology Practice Initiative (QOPI) is an oncologist-led quality improvement program that allows oncologists in academic and private settings to assess the quality of care offered within their practice. This tool could be used, for example, to help inform the NCCCP. Joint studies on quality of care in special populations could be conducted by ASCO and the NCI as well.

Although ASCO and the NCI are actively involved in their grant award programs, the cancer community must pursue ways to reduce regulatory burdens of the central Institutional Review Board (IRB) and increase the availability and reliability of information to foster research. The NCI is investing tremendously in the Cancer Biomedical Informatics Grid (caBIG™) program to help revolutionize information technology (IT) processes. There is a similar revolution in medical practice to enact routine adoption of electronic health records (EHR). ASCO has held several symposia to help practitioners adopt this practice and to help inform those who design EHR products. ASCO could play a pivotal role between caBIG™ efforts and EHR efforts to ensure that EHR products are useful for those who both practice oncology and conduct clinical research.

To continue research efforts in the future, the cancer community must collaborate to ensure the next generation of clinical oncology providers. Recruitment and retention can be fostered by conducting grant-writing and community-level clinical research workshops, mentoring programs, and more translational research professorships, and by encouraging innovative incentives, such as loan forgiveness.

Dr. Davidson stressed the need for the cancer community to carry its message of progress and impediments to the public. This is a crucial time for collaboration to clarify issues of cancer care and research costs and the return on public investment. The cancer community needs to provide evidence of its accomplishments to the public and policymakers through the Advocacy for Research Campaign and other venues. All parties need to openly discuss the barriers to research imposed by the Centers for Medicare and Medicaid Services' (CMS) new guidelines for clinical trial approval.

Questions and Answers

Dr. Runowicz asked Dr. Davidson to list her top three priorities in terms of potential collaboration. Dr. Davidson provided the following three priorities: 1) communication with the CMS on clinical trial issues; 2) ASCO's collaboration with the TRWG; and 3) standardization and unification of EHRs. Dr. Niederhuber added that he anticipates active communication and collaboration between ASCO and the TRWG because there is ASCO representation on the Clinical Trials Advisory Committee (CTAC).

Dr. Chabner asked for an update on ASCO's health disparities activities and potential cooperative relationships. Dr. Davidson informed the group that ASCO has instituted a disparities task force and that it is in the process of signing an agreement with the Susan G. Komen Foundation to deal with this issue. Dr. Niederhuber asked for clarification on Dr. Davidson's comment regarding inconsistencies in government, and Dr. Davidson explained that there are too many different layers of approval for government-sponsored trials, and that she would like to move toward a more standardized system. Chairperson Runowicz added that she has sent materials on this topic to the Chair of the Subcommittee on Clinical Investigations to review. Dr. Anna Barker, Deputy Director for Strategic Scientific Initiatives, asked if ASCO was coordinating EHR efforts with the DHHS, and Dr. Davidson replied that she would need to research that and communicate with her later. Dr. Barker indicated that DHHS is actively involved in EHR efforts and that the NCI and FDA are working through caBIG™ to further the EHR agenda. Dr. Coffey agreed with Dr. Davidson's proposed partnerships, and suggested that ASCO independently evaluate activities within the NCI. Ms. Giusti asked Dr. Niederhuber if the NCAB could

do anything to hasten the approval process through CMS, and Dr. Niederhuber replied that the NCI would not have as much leverage in advising another Federal entity as would an independent body such as ASCO.

VII. ALGORITHM PREDICTS RESPONSE TO ANTICANCER DRUGS (COXEN)— DRS. JOHN WEINSTEIN, DAN THEODORESCU, AND JAE K. LEE

Dr. John N. Weinstein, Senior Investigator and head of the Genomics and Bioinformatics Group, Laboratory of Molecular Pharmacology, Center for Cancer Research, introduced Drs. Dan Theodorescu, Paul Mellon Professor of Urologic Oncology and Molecular Physiology, University of Virginia (UVA) School of Medicine, and Jae K. Lee, Associate Professor of Biostatistics and Epidemiology and Director, UVA Bioinformatics Support Core, UVA School of Medicine, who presented research on the use of mathematics to assist with drug response. COXEN (The COeXpression ExtrapolatioN Algorithm) is an algorithm that can help predict response to anticancer drugs. COXEN was created to predict anticancer drug activity in one type of cancer based on results from a different type, or different types, of cancer.

The NCI60 panel of cell lines has been used by the Developmental Therapeutics Program for screening potential anticancer agents; to date, more than 100,000 synthetic compounds and additional natural compounds have been tested. A database of drug activity induced by those compounds in the 60 cell lines has been created. Because the NCI60 cells are extremely well characterized at the DNA, RNA, protein, metabolomic, and pharmacological levels, information on drug activity can be mapped onto the molecular characteristics of the cells. COXEN was created to permit an extrapolative prediction to cell types that were not included in the NCI60. Although the NCI60 panel serves as a useful model system, cultured cells are not ideal surrogates for clinical tumors because of a lack of contact with other cell types, cytokines, hormonal influences, and other interactions experienced by a tumor in the body. Advantages of the NCI60 cells, however, include homogeneity in lineage, manipulability, and the availability of indefinitely large amounts.

Attempts can be made to extrapolate the activity pattern of a drug in the NCI60 to other cells types using entire gene expression signatures or pharmacological gene expression signatures. Neither of those approaches works well for prediction. The COXEN algorithm goes ones step further, by generating a “co-expression gene signature” and using that for the prediction of drug activity. The results generated can be analyzed using the Receiver/Operator Characteristic (ROC) Analysis, which plots sensitivity against 1-specificity. The area under the curve provides an index of predictiveness of the algorithm. The tradeoff between sensitivity and specificity can be manipulated by choosing a high or low threshold, depending on whether more or fewer false positives and false negatives are acceptable.

COXEN is potentially useful for personalization of medicine and also for drug discovery. As a proof-of-principle project, COXEN was used to predict the activity of anticancer drugs in 40 bladder cancer cell lines (the BLA40 panel). The NCI60 panel does not include human bladder cancers, and the predictions of drug response in the BLA40 panel were performed without knowledge of drug response in those cells. Cisplatinum and paclitaxal, which are used clinically for treatment of bladder cancer, were tested in the BLA40 cells and response was predicted independently using COXEN. The correlation between the COXEN prediction and the experimentally measured GI50 value was reasonable and statistically significant for both drugs.

COXEN also was tested for the ability to predict human responses to therapy. That required clinical outcome data from patients treated for cancer with a given, single chemotherapeutic drug (not a combination of drugs) and microarray data from the patients. Two trials were selected. The first, DOC24, included 24 patients treated with neoadjuvant docetaxal. The COXEN prediction of response

showed a statistically significant correlation with clinical response—residual tumor size—after chemotherapy as defined in the trial. The second trial, TAM60, included 60 patients treated with adjuvant tamoxifen, with the clinical outcome of progression-free survival. The COXEN algorithm was able to segregate predicted responders and predicted nonresponders with statistical significance. Those two exercises indicated that COXEN can, at least in some cases, offer predictive ability for a single drug either in culture or in clinical trials.

Another use for COXEN is in drug discovery. Agents publicly available from DTP were used to generate predictive coefficients for the BLA40 cell panel; this *in silico* drug screening required use of a 30-node cluster computer for nearly 45 days. A small number of top hits then were evaluated in the bladder cancer cell lines. In particular, the top hit generated from the analysis (NSC637993) was fully evaluated in the BLA40 cell lines, and dose response curves were generated. Nearly all of the bladder cell lines were affected to some degree, although the drug had not shown high effectiveness for the nine tissue-of-origin types in the NCI60 screen. That result demonstrates how a drug that fails in certain cancer cell lines could be effective in others, and how the COXEN algorithm may permit researchers to identify effective therapies.

COXEN thus can be used to develop new drugs or leads for a variety of cancer types, limited only by the availability of gene array information for a particular cancer. COXEN also may be useful in the field of personalized medicine to predict optimal therapy for patients and test the predictions in tissues removed at biopsy or perhaps circulating cells present in body fluids. The goal is to reduce the drug attrition rate and improve the drug discovery timeline by prioritizing potential therapies.

The current top priority for COXEN is to validate the algorithm on additional use cases. A number of collaborations are underway, including a clinical trial to examine a derivative of the top hit in the BLA40 screen (NSC637993) in bladder cancer as second line chemotherapy. A Phase 2 clinical trial also is in preparation for personalized medicine in patients for whom initial chemotherapy failed. Efforts are underway to generate data on mechanisms of actions for the hits obtained from the BLA40 screen. The activity of those drugs was validated in the BLA40 cells, and promising compounds were examined using yeast chemical genetics and the TAG4 bar-coding system to understand better how they work and to identify and understand rational drug combinations that could be created using them. That may prove an effective way to prioritize drugs that should be tested in xenograft experiments and then evaluated in more detail by ADME/TOX studies. A Web site is in development to make COXEN available to the scientific community. Investigators are encouraged to enter their microarray data and use COXEN to discover or validate drugs using their own systems or to validate or examine their clinical trial results.

Questions and Answers

Dr. Runowicz asked Dr. Theodorescu how he would address the issue of complexity and heterogeneity in tumors. Dr. Theodorescu answered that COXEN has demonstrated that, despite the significant heterogeneity and differences between tumors and cell lines, there are a series of gene expression signatures that are fundamental to both. Regarding differences in drug sensitivities between primary tumors and metastases, differences are likely and the planned clinical trials will address analysis of tumors that have failed chemotherapy. The tumor that has recurred will be analyzed, rather than the original tumor. Dr. Runowicz asked how necessary samples could be obtained from patients without requiring additional surgeries. Dr. Theodorescu answered that the analyses can be performed using samples from a fine needle aspiration (FNA), although that is not ideal. A goal is to use circulating tumor cells (CTA) for analysis.

Dr. Anthony Atala, Director, Wake Forest Institute for Regenerative Medicine, and Professor and Chairman, Department of Urology, Wake Forest University School of Medicine, noted the different types of heterogeneity in cancer, such as tumor versus stroma, proliferating margins, hypoxic versus non-hypoxic areas, and stem cells. That heterogeneity points to a need for continued experiments in cultured cells, despite their limitations. Dr. Lee commented that the results from COXEN are usually heterogeneous. For example, when the COXEN algorithm was used to analyze the FDA-approved compounds in the BLA40 bladder cancer cell lines, the different cell lines responded differently to the various compounds. He agreed that understanding heterogeneity will be necessary for improving patient treatment. Dr. Niederhuber asked if Dr. Theodorescu had any concerns about the heterogeneity of the cell lines themselves. Dr. Theodorescu answered that he is aware of issues with mislabeling of some cells lines and takes care to create frozen stocks of cells and have reproducible endpoints in his laboratory. Dr. Weinstein said that over the past 3 years, several instances of mislabeling and misidentification have been found in the NCI60 cell panel and have been corrected. Appropriate molecular fingerprinting of the cells is available. There is at least one cell line that has potential heterogeneity that is being analyzed.

Dr. Lee explained that information on signatures and biomarkers gleaned from cell lines likely will be useful for tumors from patients as well. Dr. Weinstein commented that the data from different cell lines could be useful for using COXEN to extrapolate results between different tumor types. A drug that is effective for a particular type of breast cancer also could be useful for another, different type of cancer.

Dr. Atala asked if Dr. Theodorescu had plans to catalog the patient tumors and analyze the data to rely more on the use of human tumor samples in the research, as opposed to cell lines. Dr. Theodorescu answered that the original publication did evaluate human tumors and he did have plans to catalog additional tumors. Additionally, efforts are underway to use COXEN to analyze the effects of combination chemotherapy on human tumors, which will permit use of data from a larger number of clinical studies. Data from trials using combination chemotherapy can be used to train the algorithms how to predict novel combinations. He emphasized that validation will be a key step in proving the utility of COXEN.

Dr. Judah Folkman, Director, Vascular Biology Program, Children's Hospital of Boston, and Julia Dyckman Andrus Professor of Pediatric Surgery and Professor of Cell Biology, Harvard Medical School, Karp Family Research Laboratories, explained that all tumor cells are dependent on endothelial cells and many standard chemotherapeutic agents, such as cyclophosphamide and tamoxifen, effectively stop proliferation in endothelial cells, but only when given as a continuous low dose, rather than at the maximum tolerated dose. When Lewis lung cancers in mice are treated with a maximum tolerated dose of cyclophosphamide, the tumors become drug resistant and the mice die. However, treatment with cyclophosphamide at a lower dose, delivered in drinking water, eradicates the tumors. Thrombus formation by endothelial cells arrests the cells' growth. Cyclophosphamide in drinking water at a low dose increased thrombus formation four-fold in the endothelium of tumors. Knocking out one specific gene resulted in a failure to respond to cyclophosphamide. Taxol also has been found to depend on endogenous angiogenesis; taxol raises endostatin levels and is ineffective in endostatin knockout mice. All tumors are dependent on angiogenesis and there is less heterogeneity in endothelial cells, which could make these cells useful for studies of drug efficacy. Dr. Theodorescu explained that he has already initiated work to use COXEN to identify agents that could be used for metronomic chemotherapy. Technical issues such as appropriate cell lines and dosages must be resolved, but if the predictive algorithm is successful, it could permit mining of drug databases for both the cancer and the endothelial supporting structures.

Dr. Chabner commented that information is accumulating that suggests that some lung cancers share similarities with tumors in other organs. Subtypes of other cancers, such as breast, also exist, and

the original NCI60 cell panel likely does not represent all subtypes of cancer. Therefore, panels that reflect the biology of other subtypes of cancer are needed. He continued that for the newer, molecularly targeted drugs, attempts have been made to personalize treatment based on understanding receptor mutations and pathway activation that render the tumors sensitive or resistant to the drugs. He asked for comments on how that type of information would be incorporated into COXEN. Dr. Theodorescu answered that the 40 cell lines in the BLA40 cell panel are almost all from invasive, metastatic bladder cancer and are fairly homogeneous in terms of biology and behavior. Dr. Weinstein added that they also are working with a set of 25 different ovarian cancers; most are serous but one or two are clear cell tumors. He also described a recent publication presenting an algorithm called LeFE, which can use gene expression profile information to predict which Gene Ontology categories are related to a drug's activity. The LeFE algorithm can be highly predictive in moving from individual genes to pathways and systems. Dr. Lee noted that Dr. Lee Hood claims that there are networks rather than pathways, and those pathways respond to the environment and cancer. He suggested a small experiment to assess predictiveness of COXEN regarding a vaccine, using only information relevant to that pathway. Responsiveness could be predicted only if information from genes from neighboring networks were included.

Dr. Coffey described problems with using established cell cultures. Primary cell cultures select for the most rapidly growing cells; once maintained in culture for 10 or 15 years, the cells are significantly different from the cancer from which they originated. Xenografts were thought to be a solution, because they allow the tumor to interact with stromal epithelium; however, solid tumor xenografts did not predict clinical results. He asked if data could be obtained from the clinical tumors and applied to the algorithm to work back and determine whether any models had patterns similar to that of the clinical tumor. Beginning with tumor cells might help identify relevant genes for drug response. Dr. Weinstein agreed that reversing direction to determine which models have predictiveness using COXEN could be a productive approach. Dr. Theodorescu agreed and noted that COXEN could be used to deconvolute information obtained from human material taken during the course of a clinical trial along with associated Affymetrix data; the information then could be used to predict results from a second trial or identify xenografts that are suitable models. He acknowledged that it can be difficult to use COXEN for drug discovery when only a few cell lines are available, as is the case in prostate cancer. Dr. Weinstein agreed, but added that cultured cells are useful because they can be manipulated genetically and analyzed for their resistance. The information from pharmacological studies on cell lines can be analyzed using COXEN in an attempt to predict results of clinical trials.

Dr. Barker commented that this work could be useful for TCGA for genome characterization and sequence comparison among human specimens and between communities such as the epigenomics community, transcriptome community, and so on. There are thousands of cell lines available, but the COXEN work could help identify which would be most useful to include in studies.

VIII. MINI-SYMPOSIUM: STRATEGIC PARTNERING TO EVALUATE CANCER SIGNATURES (SPECS) PROGRAM—DRS. JAMES DOROSHOW, JAMES W. JACOBSON, MATTHEW J. ELLIS, WING C. CHAN, AND CHERYL L. WILLMAN

Introduction. Dr. Doroshow provided a very brief overview of the Strategic Partnering To Evaluate Cancer Signatures (SPECS) Program. He explained that SPECS is a follow-on initiative from the successful Director's Challenge Program, which demonstrated that it is possible to develop molecular classifiers for cancer as well as showed the correlation of molecularly identified subsets of cancers with different clinical outcomes. The vision of molecular diagnostics for personalized medicine is based on the idea that molecular signatures of gene expression, protein expression, and genomic alterations can guide treatment decisions. Challenges of moving molecular signatures toward clinical applications involve: refinement of the signatures, confirmation and validation of signatures in independent sets of

clinical specimens, and the development of robust clinical assays and prospective validation of the clinical utility of the signatures. Other obstacles include the difficulties of conducting evaluations in an environment of rapid evolution of both technologies and clinical practice, as well as multi-institutional collaborations that are required to bring together the critical expertise and resources for refinement and validation of the signature. Dr. Doroshow next introduced Dr. James W. Jacobson, Program Director, SPECS, and Chief, Diagnostic Biomarker and Technologies Branch, Cancer Diagnosis Program, who described several noteworthy projects in the SPECS Program.

Dr. Jacobson said that the SPECS Program established several objectives to meet the challenges, including to: translate molecular signatures to improve treatment selection and patient outcomes; establish strategic partnerships that bring together the interdisciplinary teams needed to evaluate the clinical utility of molecular signatures; evaluate molecular signatures previously correlated with important clinical parameters; confirm and refine the signatures; and develop robust, reproducible assays that can be incorporated into clinical validation trials. Six projects have been funded by SPECS. Dr. Jacobson noted that three of the projects will be described by their investigators, but that he would first present highlights about the other three programs.

Signatures of Common Childhood Sarcomas. Dr. Timothy J. Triche, Children's Hospital, Los Angeles, leads this project, which is focused on developing signatures of outcome in sarcomas. Two of these are a gene expression signature that improves diagnosis of rhabdomyosarcoma and one that predicts outcome. The project also aims to evaluate signatures of outcome for osteosarcomas, Ewing's sarcomas, and nonmyogenic soft tissue sarcomas. The project has been able to demonstrate using these powerful molecular techniques that there is a subset of the alveolar rhabdomyosarcomas that do not contain the signature translocations that involve a PAX gene with the FKHR gene. Their molecular signatures do not cluster with the other translocated alveolar rhabdomyosarcomas but instead cluster separately with the embryonal rhabdomyosarcomas. This has tremendous impact in terms of how these patients actually get treated as they likely are being significantly overtreated because they clinically and biologically behave more as embryonal rhabdomyosarcomas; discussions are ongoing within the COG as to how to bring this into the next round of clinical evaluation within the COG. Additional research has produced a cleaner outcome predictive model that has improved the accuracy and certainty of predictions over more subjective evaluations of the potential outcome for patients using standard clinical parameters. There is a synergy occurring among the COG, NCI, and Department of Defense (DoD) that leverages the investment in the sarcoma SPECS by combining gene expression signatures and evaluation of chromosomal abnormalities in order to identify potential therapeutic targets. Efforts are underway to find the resources to bring these projects together as the next childhood TARGET project.

Signatures in Prostate Cancer. A second program is a prostate cancer program with Dr. Dan Mercola, University of California at Irvine. A large consortium of universities and institutes is involved, including the Northwest University Prostate SPORE, TGEN in Phoenix, and two community-based health care organizations. Additionally, collaboration is ongoing with Althea Technologies, which is helping develop their clinical assay. The project is working to refine gene signatures that predict the outcome of prostate cancer patients. This has involved the development of signatures that exhibit differential expression of genes from both tumor and stromal cells that separate patients who relapse from those who do not relapse. It is easier to identify early relapsers. Dr. Mercola also has shown that classifiers built in different ways from the same data set predict relapse well but share no genes. He further took 1,500 genes that have been shown to be differentially expressed between relapsers and non-relapsers and refined the gene set on two published datasets. Through a decision tree analysis of one dataset, he ended up with a signature of 15 genes that was able to predict those that would relapse early. In the other dataset, Dr. Mercola ended up with a signature of 10 genes. He then cross-validated them on the opposite dataset and ended up with 6 and 7 genes in two analyses that clearly predict who will relapse early. The clinical

outcome from those two studies reveals a broad separation between those that will relapse early and those that have stable disease. The study involved approximately 80 patients that ranged in Gleeson score from 4 to 10, with most between 6 and 8. Sixty patients in the validation study were representative of prostate cancer patients.

Signatures in Lung Cancer. Dr. David P. Carbone, Vanderbilt-Ingram Cancer Center, heads the SPECS project addressing lung cancer. He also serves as the head of the Vanderbilt Lung SPORE and has brought into his collaboration investigators from all five of the other lung SPORES. Other collaborators include a number of academic institutions, a small company that specializes in data analysis, the Southwest Oncology Group (SWOG), and an international collaborator from Barcelona. The research focuses on the use and validation of the proteomics platforms with primary focus on use of various mass spectrometry strategies. Dr. Carbone has been careful in defining reproducibility and performing cross-institutional validations, and he has looked primarily at three areas: serum proteomics profile to assist clinical decision making in patients with suspicion of disease; proteomic profile of tumors to predict metastasis and death; and serum proteomic profiles that predict response to EGFR inhibitors. The study to predict response to EGFR inhibitors involved patients from Italy and Japan who had been treated with an EGFR inhibitor. A cross validation was performed, and the eight-peak predictor was tested on two independent cohorts that had been treated with an EGFR inhibitors, one from Italy and one from ECOSOG. The predictor performed well in both of those cohorts. Importantly, three datasets from patients who had never seen EGFR inhibitors were analyzed and the predictor was unable to stratify these patient populations. Dr. Carbone has also conducted a cross-institutional validation of the robustness of the technology. Using protocols developed at Vanderbilt University and the same mass spectrometry instrumentation, researchers at Vanderbilt and the University of Colorado showed a high concordance between the two institutions with almost perfect correlation—only 6 out of 200 patients were discordant. Analyses of biopsies also are planned to build more information to refine these signatures and make them even more robust. The project also is developing signatures that combine proteomic, genomic, and gene expression data.

Dr. Jacobson then introduced three investigators who would each describe his/her SPECS Project: Drs. Matthew J. Ellis, Washington University; Wing C. Chan, University of Nebraska Medical Center; and Cheryl L. Willman, University of New Mexico.

Questions and Answers

Dr. Coffey asked for clarification about Dr. Mercola's cross comparison of genes and those that were the final predictors. Dr. Jacobson explained that a large number of genes were present, and that a number of decision trees were used to separate the populations to help with prediction of disease outcome.

Biological Breast Cancer Classification by qRT-PCR. Dr. Ellis said that breast cancer is generally treated as more than one disease and is currently classified by two biomarkers: estrogen receptor measurements and HER2 over expression/amplification, which generates four subtypes that drive clinical practice. Endocrine therapy is an important focus of ER+ disease and trastuzumab is an important focus for HER2+ disease. There is more specific use of polychemotherapy across the subtypes. For HER2+ disease, questions remain as to why trastuzumab does not cure everyone and whether failure can be predicted. In the endocrine therapy field, many patients are believed to be overtreated with chemotherapy, and there is interest in determining which patients can be treated only with endocrine drugs. The biologic orphan of the ER-/HER2- subtype also poses many questions.

An experiment conducted by Drs. Therese Sorli and Chuck Perou using DNA microarray analysis was able to identify different subtypes of breast cancer with clinical significance. Several groups of tumors were categorized: luminal A, B, and C, and basal. Luminal A had a relatively good outcome. Luminals B and C comprised a group of ER+ tumors in which, despite heterogeneity, they were doing more poorly. The basal group expressed transcripts typical of basal epithelium, and they do particularly poorly. These datasets grew over the years, and researchers began to think about developing clinical grade tests that could identify these subtypes. As datasets grew to very large sample sets in excess of 500 to 600 cases, the robustness of these signatures became apparent.

The grant for the SPECS Project included a "working formulation" that identified four ER+ subtypes (all luminal) as low risk, high risk HER2+, high risk HER2-, and uncertain risk. The ER- subtypes included ER-/HER2- (basal), ER-/HER2+, and several other subtypes. The Project consortium includes the Washington University in St. Louis, University of Utah, University of British Columbia, University of North Carolina, and Cancer and Leukemia Group B (CALGB). The project principles were to: develop a robust clinical assay that could assist in clinical decisionmaking based on biological subtyping; use technologies that could be translated rapidly into clinical use because they form the basis of approved assays in other fields of medicine; format the assay for archival formalin-fixed tissue for rapid validation and without the need to obtain frozen tumor materials; and develop a commercialization strategy early on.

Key steps for the qRT-PCR format were to reduce the number of genes to a minimum set and develop an assay for the old tissues. Then testing occurred in three phases: 1) testing in uncontrolled cohorts of a full spectrum of patients, 2) testing in cohorts with more defined subsets in clinical questions, and 3) testing in randomized trials. In terms of gene prediction, the research has identified 50 genes to differentiate between luminal A, luminal B, basal and HER2 positive breast cancer with a good separation of the A-B curve. This predictor works for relapse-free survival and overall survival, as shown by data from the Netherlands Cancer Institute. In terms of relationships with standard markers, such as ER, this predictor correctly identified clinically ER+ tumors, as well as a few basal tumors that were typed ER+ by a clinical assay, suggesting that this assay also has the potential for spotting false positive ERs. Test sets showed that the A-B distinction works for pure prognosis in ER+ disease and in the presence of endocrine therapy, and they separated out the ultra poor prognosis patients; 20 percent of the patients in this so-called good prognosis A signature group, however, still relapsed.

To develop robust reagents, the research focused on identifying oligonucleotides that worked for qPCR in old FFPE samples by comparing the archival frozen samples from a particular tumor with the patient-matched, archived formalin-fixed block. Ultimately, the research profiled 305 invasive breast cancers from the FFPE blocks by qRT-PCR. The basal-type group was marked by very high levels of the "proliferation" genes, which appear in the luminal B group and not in the luminal A group. The presence or absence of this proliferation signature is a key aspect of the difference between good and poor prognosis in ER+ tumors. To make the assay clinically useful, each sample was correlated by its group (e.g., luminal A) and by its relationship to the other subtypes; this information fed into a computational model that summed the hazard ratios to produce a relapse risk coefficient. Basal, HER2, and luminal B tumors always have a high risk score. A group of tumors called luminal A prime appear to have a very low risk score. This approach was successful in identifying, in a test set, Stage 1 breast cancer patients on tamoxifen who have very low risk, and this information will be helpful for patient treatment.

The project's next steps involve work with: the University of British Columbia tamoxifen series; a randomized trial of paclitaxal versus observation spearheaded under CALGB; issues of commercialization and IP, and incorporating novel therapeutic target assessment, with particular attention to PI3CA kinase domain mutations and outcome.

Dr. Ellis concluded with the six overall project results: 1) a prototype breast cancer biological sub-classification assay has been established that provides independent prognostic information and patent filed; 2) gold-standard oligos and samples have been developed; 3) datasets are in place for validation for the prognosis in the presence of tamoxifen; 4) a commercialization strategy has been agreed on by the Universities involved in the grant and University Genomics; 5) new advances in DNA profiling are being built into the assay; and 6) negotiations are underway with sub-licensees to develop an IVDMIA.

Questions and Answers

Dr. Chabner requested more details about the assays and their availability. Dr. Ellis said that the two subtyping assays currently in commercial use are MammaPrint, which the FDA recently approved, and Oncotype. Oncotype is subtyping only ER+ tumors and MammaPrint requires frozen tissue and so there is an opportunity for an assay that subtypes across the entire spectrum of breast cancer that can be validated with archival paraffin embedded tumor material. Dr. Chabner asked whether a trial is planned to compare molecular subtyping assays prospectively. Dr. Ellis replied that he serves as the Correlative Science Chair of a committee looking at the TayloRx trial, which is based on prospectively looking at the Oncotype DX assay; it would be an ideal format in which to conduct such a comparison, and the intent is to propose such work once the assay moves beyond prototype stage.

Ms. Giusti asked about the project's funding structure and sponsors other than the NCI. Dr. Ellis answered that the Breast Cancer Research Foundation provided seed money that allowed the research to generate data on the qRT-PCR capacity. Data and samples from the Cooperative Groups' trials also represent a large investment that helped the project.

Dr. Coffey asked whether cross validation, similar to the technique used in the SPECS prostate project, had been performed to determine whether a small number of therapeutic predictors were present. Dr. Ellis agreed that adding a true response predictor of endocrine therapy would provide an extraordinarily powerful tool for diagnosis and therapy, and he referred to an ongoing prospective trial of neo adjuvant endocrine therapy called Z1031, supported by the American College of Surgeons (ACS). Dr. Coffey also queried about the application to prevention trials. Dr. Peter Greenwald, Director, Division of Cancer Prevention, said that, from the first breast cancer prevention trial with tamoxifen, Dr. Su Paik, Head Pathologist, has been studying quantitative ER by looking at proteins in mRNA, and he has found that those that were resistant to tamoxifen had low levels of ER+. Dr. Coffey stated that it would be interesting to look at this different tumor biology in terms of prevention, treatment and diagnostics, and relapse.

Molecular Signatures to Improve Diagnosis and Outcome Prediction in NHL. Dr. Chan began his discussion of NHL by sharing data about lymphoma, which had been prepared by a member of the SPECS team for legislators and used his wife's case as an example, illustrating why pathologists need to perform immunostaining at the time of diagnosis of lymphoma. He explained to the senators and congressmen that an accurate diagnosis of lymphoma is needed and, in addition, that patients would like to know their prognosis. Furthermore, the clinician would like to obtain guidance on the most effective therapy for a given patient. Currently, a number of immunostains are employed in an attempt to provide the desired information. Dr. Chan said he would present some of the project's findings in diffuse large B cell lymphoma (DLBCL) to illustrate what the SPECS Program has achieved in this direction.

A large consortium of universities and institutions comprise the project, as well as NCI's intramural program. These include the University of Nebraska Medical Center, the University of Barcelona (Spain), the University of Wurzburg (Germany), Radium Hospital (Norway), St Bartholomew

(England), British Columbia Cancer Agency (Canada), and four institutions in the Southwest Oncology Group (SWOG). Such a large consortium will provide significant tissue resources (from different areas and clinical settings) and different expertise, and the assay will be performed in different institutions.

Prior studies, including Dr. Chan's work under a Director's Challenge grant, used gene expression profiling to look at a large group of B-cell lymphomas and were able to derive robust signatures to differentiate at least three types of DLBCL, called the activated B-cell type, germinal center B-cell type, and primary mediastinal B-cell types. These types could be readily divided by gene expression signature, and the large cell lymphoma also could be separated from another aggressive B-cell lymphoma, Burkitt lymphoma. The subset differentiation is important for outcome prediction because patient survival data show that, in germinal center B-cell type and primary mediastinal large cell type, there is relatively good prognosis and the 5-year survival is approximately 60 percent. In the ABC type, however, patients have significantly poorer survival and the 5-year survival is only about 30 percent.

Heterogeneities exist within the subtypes, and there are three additional signatures that are important in predicting survival in large cell lymphoma. These are: 1) MHC Class II genes, in which low expression is associated with a poor outcome; 2) a large group of genes representing the lymph node signature (or the stromal signature) of the lymphoma, in which high expression is associated with good outcome; and 3) the proliferation signature, in which high expression is associated with poor outcome. The study has suggested that host interaction with the tumor, as represented by the MHC II and lymph node signatures, is likely important in the survival of patients with DLBCL.

In mantle cell lymphoma, there is one major signature that is important in predicting survival, which is a proliferation signature that can be represented by 22 genes. Whereas in large cell lymphoma and follicular lymphoma, the host-tumor interaction appears to be very important, the biology of the tumor is of major significance in mantle cell lymphoma. In a study that divided patient groups with mantle cell lymphoma according to the proliferation signature into four quartiles, patients with a high proliferation signature had very poor median survival of less than 1 year, while patients with the lowest proliferation signature had indolent disease and a median survival of approximately 7 years. The proliferation signature, therefore, identifies patients with a substantial difference in survival.

The project has established a partnership, negotiated by the NCI Technology Transfer Office, with Roche Diagnostics. The negotiation process was highly transparent and fair to both the company and the institutions. Roche has agreed to provide additional resources and expertise to the consortium, such as the expertise of reagents standardization, assay optimization, protocol development, personnel training, and proficiency testing. The collaborative effort will try to develop a diagnostic array for FDA approval in about 2 to 3 years.

Dr. Chan next described the new study on DLBCL conducted over the past 2 years. In 2000, Rituximab, an antibody against CD20, was introduced into the treatment regimen for DLBCL; it was first reported to be useful in advanced stage DLBCL and significantly improved the prognosis in this group of patients. It is now the standard of care for all DLBCL patients and has a significant influence on the treatment outcome. With the change in treatment from combination chemotherapy like CHOP to the current regimen with Rituximab, previously defined prognosticators need to be re-examined. Dr. Chan presented data that showed that the survival curve for DLBCL patients who were treated with Rituximab plus CHOP; the prognosis was significantly improved over those treated with CHOP alone. The study looked at a new group of 156 patients with *de novo* DLBCL who had been treated with Rituximab plus a CHOP-like regimen. All cases were reviewed to confirm the diagnosis of DLBCL, and then the two largest subgroups, GCB and ABC, were examined because there were enough cases to look at prognosticators. Three of the four previously defined signatures are still predictive of outcome, but one

dropped out. The prognosis improved for both DLBCL subgroups (GCB reached approximately 80 percent survival and ABC about 60 percent), but the subtype distinction is still significant. In addition, patients with low proliferation signature still had significantly better survival than the group with high proliferation signature.

Toward the end of Dr. Chan's prior research under the Director's Challenge grant, some of the genetic abnormalities in DLBCL appeared to be associated with better prognosis and some with poorer survival: specifically, the gain of the short arm of chromosome 3 is associated with poor survival independent of the gene expression defined prognosticator. The SPECS Project proposed to use DLBCL as a model to examine the relationship of genetic abnormalities to outcome and see whether they can be incorporated into a prognosticator.

Dr. Chan's group has completed a study of approximately 200 patients using a high-resolution microarray platform looking at comparative genomic hybridization that can define gain and loss of segments of chromosomes at a very fine level. Three major subtypes of DLBCL were examined. Findings include that the different subtypes of large cell lymphoma have different profiles of genetic abnormalities. Numerous gains and losses were detected, and Dr. Chan highlighted the frequent gain or amplification in 19q in the ABC type with a presumptive target gene of SPIB, which is a transcription factor. Another interesting finding is that 13q amplification or gain in DLBCL appears almost exclusively in the GCB group and not in the ABC group.

At the end of the grant cycle, this SPECS Project is expected to have a diagnostic array for NHL ready for FDA approval, as well as to have found reliable signatures that can identify disturbed functions in many molecular pathways that may be useful in predicting response to pathway-specific therapy when available. In addition, the study will have accumulated a large data/tissue resource that is available for continued discovery process to help reach the goal of individualized medicine in the future.

Questions and Answers

Dr. Chabner questioned the possibility of having a diagnostic test on which to make therapeutic decisions within the next 2 to 3 years and asked for an example of a therapeutic decision that likely would be made based on the arrays. Dr. Chan said that the distinction between Burkitt and large cell lymphoma is important and the array could help differentiate borderline cases better than what is currently achievable. Moreover, mantle cell lymphoma can behave indolently and may be treated quite differently from the more aggressive cases as identified by the proliferation signature. Drs. Niederhuber, Chabner, and Chan agreed that the array potentially could guide treatment.

Discovery of Molecular Classifiers for Outcome Prediction and Novel Therapeutic Targets in High Risk Pediatric Leukemia. Dr. Willman indicated that this SPECS Project was a follow-on activity from the NCI Director's Challenge grant, and her laboratory has several projects that are focused on adult and pediatric acute lymphoblastic and acute myeloid leukemia. She focused the presentation on work looking at interesting new targets for therapy in children with high-risk pediatric acute lymphoblastic leukemia. Consortium members include the University of New Mexico Cancer Center, Fred Hutchinson Cancer Research Center, NYU Medical Center, COG, and SWOG. Approximately 75 to 80 percent of children with ALL achieve long-term survival. The studies have provided an interesting clue as to why Hispanic and Black children treated on the same treatment regimen have poor treatment outcomes, which Dr. Willman said she would explain a bit later.

For these studies, currently all children with ALL receive the same treatment for the initial 30 days of their care so that samples that come into the laboratory have 30 days of intensive induction

chemotherapy and undergo many genetic assays in the laboratory in an attempt to determine the genetic abnormalities that exist in the leukemic blast. Through a nice Web-based informatics system, the laboratory collaborates with institutions to pass back that genetic data on children who have been standardized on lower, intermediate, or more intensive therapies for the remainder of their treatment course. Despite these therapeutic advances, the children continue to be treated with the same therapy for the initial 30 days, followed by further therapeutic intensification of largely the same drugs. Based on some common genetic abnormalities in children, trisomies of several chromosomes (e.g., the TEL-AML1, the 12;21 translocation) respond well to current therapies, and then a progressive failure to respond well occurs to a whole series of different therapies. Approximately 25 percent of children relapse; for nearly 30 percent of children with higher risk disease, genetic abnormalities have not been uncovered, and these children do not respond well to current treatment regimens. The challenges in pediatric ALL include identifying those children who could be cured with less intensive therapies and fewer long-term side effects, and uncovering the underlying genetic abnormalities in this resistant form of disease and identifying new targets for therapy.

The project selected a cohort of more than 200 children with high-risk ALL who were uniformly treated on a trial called COG9906 using an augmented BFM regimen from Europe, which is an aggressive therapy. There was a male predominance in the trial. In addition, nearly 25 percent were Hispanic, providing some statistical power to begin to model what might be going on in these children. A small number of Black, Asian, and Native Americans were included as well. Most of the children were older and tended to have higher white counts; overall, the 4-year event-free survival on this trial was 61 percent. The approach was to perform comprehensive gene expression profiling of a pre-treatment leukemic sample and use sophisticated statistical and high-performance computational tools for data analysis and modeling.

Dr. Willman described a collaborative effort spearheaded by the COG coordinated project TARGET that has brought together independent researchers in a comprehensive molecular analysis of high-risk ALL, with a significant use of caBIG™. The research focused on trying to identify novel cluster groups of high-risk ALL patients who share common gene expression profiles, as well as modeling sets of genes that are predictive of overall outcome at diagnosis and bringing this information into COG trials. A clustering algorithm developed by Sandia National Laboratory, called VxInsight™, was used for building "terrain maps" of complex genetics for visualization. This tool allows researchers to work with all of the genes, rather than limiting to perhaps 200, and thus avoids bias; it clusters patients in mountains based on similarities of gene expression profiles and performs rapid statistical analyses that inform researchers of the genes that distinguish a given group. The high-risk ALL children in the study were not genetically homogeneous; seven distinct types of gene expression profiles were found. Some of the children had a 119 translocation involving two genes, others had abnormalities of the MLL gene on chromosome 11, and eight previously had Down Syndrome. Next, a novel statistical technology was developed based on an outlier analysis to identify genes that always track together but are barely highly expressed and probably reflect an underlying chromosome translocation; this also resulted in seven cluster groups. The overlay between these two methodologies is the same. Dr. Willman described two interesting cluster groups, Clusters B and F. The outcome between these two groups was dramatically different: Cluster B contained older children with a low white blood cell count who had an incredibly good outcome for the disease. Further studies by NCI-supported researchers at St. Jude's Hospital, which will be publicized at ASH, have discovered an underlying genetic abnormality in this group of children that might serve as a new therapeutic target. Cluster F has an outcome of 18 percent in 4 years and is 0 percent at 5 years so far; nearly all of the Hispanic children in this cohort are in this cluster, indicating racial heterogeneity in terms of response.

The TARGET Consortium is now filing patents for new targets in the children who do extremely well and those who do extremely poorly. One of these is a gene called CRLF2, which appears to be an important adhesion molecule that modulates the effect of the IL-7 receptor, which is the key growth factor receptor for early B progenitor cells. Another gene that is being studied is the GPR110, which is a novel analog of the estrogen receptor, which is important because leukemic cells have particular steroid responses. Both of these genes are highly expressed. The project intends to make use of the NCI's Mouse Models Phase I Models Program's existing ALL animal model that has this phenotype to use in biologic studies.

Dr. Willman briefly described the computational and statistical analyses performed. Supervised learning was used to develop tests and training sets, as well as a molecular classifier. Genes were selected to predict survival at 4 years or minimal residual disease. Intense computations were made to classify for survival time in days; researchers modeled 207 outcome points times 54,000 genes, with extensive cross validation and external validation. This work is in the process of submission to the *New England Journal*.

Based on computations using a set of 43 genes, children were separated into a low risk and a very high-risk group of relapse. This was further refined by blending the molecular classifier with whether the children had minimal residual disease by flow cytometry at end induction. Four groups were defined: low molecular risk and MRD-, low molecular risk and MRD+, high molecular risk and MRD-, and high molecular risk and MRD+. These studies showed that children represented in different curves need completely different therapies. A molecular classifier was built to predict residual disease at day 30 and resulted in a 23-gene classifier that actually predicts whether a child will have minimal residual disease at day 30 or not. It has a tremendous ROC accuracy curve and has been reproducible in two other datasets. In addition, in the previous week, researchers finished the validation on a set of 100 children treated on a separate high-risk trial from the COG several years ago.

The SPEC Project's next steps are to continue evaluation and biologic studies of potential new therapeutic targets in high-risk ALL using animal models and COG patient samples, as well as prospectively test predictive classifiers for MRD and EFS in the next generation of COG trials and initiate studies in children with "good risk" ALL.

Questions and Answers

Dr. Folkman complimented Dr. Willman on the work conducted and asked whether the Downs Syndrome were equally distributed between the blue and the yellow groups. Dr. Willman confirmed that they appear all over, despite the researchers expecting them to cluster; this reveals that what is driving the leukemia is beyond the extra chromosome 21.

IX. OVERVIEW: NCI ACTIVITIES WITHIN NIH CLINICAL CENTER—DR. LEE HELMAN

Dr. Lee Helman, Scientific Director for Clinical Research, CCR, described the NCI clinical research program and outlined some of the unique resources of the NIH Clinical Research Center. The vision of the CCR is to integrate basic, translational, and clinical research to make cancer preventable, curable, or chronically manageable. Its mission focuses on the patient to inform and empower the entire cancer research community by making breakthrough discoveries in basic and clinical cancer research, and by developing them into novel therapeutic interventions for adults and children afflicted with cancer or infected with HIV. The CCR is considered unique in that it incorporates the skills of both basic and clinical scientists who work together on complex scientific problems surrounding the issues of the

biology and behavior of cancer. The CCR has the capacity to redeploy resources quickly to address new missions or urgent public needs or new opportunities informed by the larger cancer community. It also has access to the NIH Clinical Center, which is the largest clinical research center in the world. The NCI intramural clinical program is not a large-volume, full-service cancer center. Rather, it is a high-intensity cancer center focused on selected cancers and understudied diseases. It is capable of performing patient-intensive clinical research to develop new approaches for prevention, diagnosis, and treatment and is, therefore, a key component of the Nation's overall cancer program.

The integration of basic and clinical research has changed the culture of how intramural researchers work together. CCR scientists conduct concept-based, science-driven, clinical trials for evaluating new therapies rather than testing existing ones. When these trials are successful, they can be tested further in much larger studies through the extramural program. There is close integration of preclinical models and methods with early clinical development. CCR researchers are working hard to develop molecularly targeted agents and combinations that can be used in clinical trials, and they are pursuing novel approaches to early detection and prevention. The CCR will focus on testing new science-based hypotheses interrogating a disease or a disease process using genetic, proteomic, and imaging tools to maximize the science community's understanding of how to intervene in those processes.

The NCI Experimental Therapeutics (NExT) is a partnership between the NCI's DCTD and the CCR. The program has a greater tolerance of risk in approaching new therapeutic targets compared to many private-sector players because it is a government program. The increasing number of potential targets relevant to cancer treatment makes testing of all new agents and combinations very difficult outside the government-sponsored arena. NExt can involve academic investigators without being limited due to lack of current IP protection or lack of successful precedents. NExT scientists can combine resources of the intramural program with those of the DCTD to focus on early drug discovery and development.

The NExT center focuses on molecular imaging and early development of pharmacodynamic markers in the preclinical setting. Data from these studies are included in the intramural program's clinical molecular profiling core. Researchers conduct DNA and RNA profiling of patients in CCR treatment protocols and couple this genetic data with outcome data.

These data will be used to help move the cancer community toward more individualized, or preemptive, medicine, where clinicians no longer treat diseases, but treat abnormalities or the pathways to disease. Oncologists no longer will wait for a tumor to recur before continuing treatment; they will monitor patients for reactivation of the driving pathways and treat them preemptively by inhibiting the reactivated pathway. Individualized medicine increasingly will incorporate the use of imaging also, and it may be possible in the future to make initial diagnoses from images. Clearly, imaging will need to be combined very actively with preclinical models in CCR drug development efforts.

Dr. Helman closed his presentation with a brief overview of the clinical trials portfolio, treatment modalities, biologic portfolio, and organization of the clinical program.

Questions and Answers

Dr. Lloyd Everson, Vice Chairman and Member of the Board of Directors, US Oncology Incorporated, asked how many new patients were admitted annually and how the CCR advertises for them. Dr. Helman responded that CCR patients comprise about 40 percent of the overall clinical program of the hospital and that most patients have been treated primarily at diagnosis at another center and are referred to the CCR to be evaluated for either Phase I or Phase II studies. He added that the number of

CCR patients have increased 5 to 10 percent each year. In addition, the CCR puts more pediatric patients on Phase I studies than any other single institution in the country, and it has the capacity to support similar studies in medical oncology. Dr. Chabner asked how many people are on clinical trials, and Dr. Helman responded that about 95 percent of the patients are on clinical trials.

X. STRATEGIC PLAN: MEDICAL ONCOLOGY BRANCH, CENTER FOR CANCER RESEARCH—DRS. LEE HELMAN AND GUISEPPE GIACCONE

Dr. Giuseppe Giaccone, Chief, Medical Oncology Branch (MOB), presented the strategic plan for the Branch. The short-term goals are to: integrate and rationalize clinical trial efforts of the MOB and affiliates; restructure the fellowship program; restructure outpatient clinics; shorten the protocol review process; and improve collaboration with industry. The long-term goal is to have the intramural program play a major role in the development of new strategies to treat cancer. The MOB currently is recruiting research personnel for tumors from lung, breast, head and neck, and gastrointestinal cancers; it already has well established programs for prostate cancer and lymphomas. The MOB is poised to research rare cancers such as adrenal cancer, cutaneous T-cell lymphoma, and thymoma using genomic approaches. The NCI MOB engages in Phase 0, I, and II clinical studies, and differs from other MOBs in four major ways. The NCI MOB accepts patients for clinical studies from all over the United States, while other MOBs generally enroll local patients only. The NCI MOB is a research institute, with 95 percent of patients enrolled in clinical studies; it researches rare tumor types and engages in early drug development studies. In contrast, other MOBs serve mainly a patient clientele, with a small percentage of those patients enrolled in clinical studies. Also, they generally work with more common tumor types and are engaged in both early and late drug development studies.

The strategies of the NCI MOB include utilizing internal development to bring molecular oncology and novel targets to the clinic; the extensive use of genomics to select patients and identify mechanisms of action; engaging industry to run unique biomarker and imaging studies; developing novel assays and statistical designs for clinical studies; and collaborating with extramural programs. Dr. Giaccone plans to conduct regular meetings on targeted therapies, in collaboration with the NDDO Research Foundation and the European Society for Medical Oncology. The next meeting will be held in Bethesda, MD, back-to-back with the Cancer Therapy Evaluation Program (CTEP) Phase I meeting, but alternating sites for future meetings between Bethesda and another site in Europe.

Dr. Giaccone described the Centers of Excellence as focal points for bench-to-bedside translation; they support the IRB's dedication to long-term, high-risk, innovative basic, clinical, and epidemiologic research. Five trans-Institute centers have been organized under this umbrella: immunology, chromosome biology, HIV/AIDS and cancer virology, molecular oncology, and molecular epidemiology. The Centers of Excellence in molecular oncology, involving a partnership between the NCI MOB and the NCI Experimental Therapeutics program, encompass assay development, screening MTDP, natural products, preclinical models, chemistry and structure biology, genomics, imaging, and pharmacokinetics/ pharmacodynamics.

Dr. Giaccone next described some of his work on EGFR mutations in relation to nonsmall-cell lung cancer. The conclusions of his study show that the YFP-EGFR ICD constructs, combined with immunofluorescence using phosphor-specific antibodies, represent a simple and useful system to evaluate the effect of novel cancer-associated EGFR mutations rapidly. The assay also can be used to test the response of different EGFR variants. In addition, some EGFR mutations do not result in constitutive activation of the receptor, and some of the changes are likely polymorphisms. Future plans include testing of other TKIs, such as irreversible TKIs; testing novel EGFR variants, such as E884K, reported to

be resistant to erlotinib but sensitive to gefitinib; and testing agents that may reverse or circumvent resistance to EGFR inhibitors, such as HSP90 inhibitors.

Dr. Giaccone said that survivin, an anti-apoptosis gene, is a potential target for cancer therapy because of its high frequency of expression in lung, bladder, pancreatic, colon, breast, ovarian, and prostate tumors and lymphoma. Survivin overexpression correlates in some cancer types with poor patient prognosis. He suggested that blocking the expression of survivin may restore default cell-death checkpoints and/or impair cell division, selectively eliminating cancer cells. He reported on the attempts to develop novel survivin inhibitors, utilizing the dymerization characteristics of this molecule, which is essential for the nuclear/cytoplasmic shuttling of the protein.

Questions and Answers

Dr. Chabner asked about MOB fellowship, staff, and resources and their relation to other branches within the clinical program. Dr. Giaccone said that it recruits 10 fellows each year, for a minimum of 2 years; whereas most fellows continue for 3 years, some stay for 4 years. The fellows are located on the NIH campus to learn research and at the Naval facility, where they encounter more general practice and clinical care. The MOB has 22 nurse practitioners and 30 research nurses who report mainly to the MOB, but who are available to other branches as needed. The resources of the Medicine Branch are all integrated with the staff of the Naval facility. Dr. Chabner asked if there are other medical oncologists working for other branches. Dr. Giaccone confirmed this. The oncologists for other branches are affiliated with MOB, and protocols are being reviewed within the MOB to standardize operations and reduce redundancy of effort. Dr. Niederhuber added that the challenge is to try and integrate resources, not destroy them, and the willingness of the staff to adapt is evident.

Dr. Chabner also asked what some of the hurdles were for the MOB and what the NCAB could do to help. Dr. Giaccone responded that there is a need to make the MOB more attractive to recruits by making things more competitive with other institutions, in relation to salary and ethics guidelines. Dr. Niederhuber said that strides are being made, but that NCAB may be able to help articulate to Congress the need for the NCI to become closer to the academic community in terms of these issues. Dr. Chabner noted that MOB salaries are relatively competitive and that staff have the advantage of being funded, without having to solicit their own research funds. He suggested that the NCAB could support the fellowship program and suggested a separate retreat to discuss fellow recruitment. Dr. Helman raised the issue of owning stock in pharmaceutical companies and the ethical considerations for recruiting those who own it. Dr. Atala asked about the MOB's work in terms of retention and requested clarification on how to approach Congress regarding competitive salaries. Dr. Niederhuber explained that education is needed regarding the differences between universities and the NIH, as well as how the NIH competes with academia for funding. Oversight committees could be developed to help put ethics regulations in place, just as they do in academic institutions. Dr. Folkman asked whether a trans-NIH initiative existed to deal with recruitment and retention, and Dr. Niederhuber said that the NIH is working on the issue, but that the NCI needed to address the issue of retention more aggressively. He noted that recruitment was not a severe problem, but retention posed more of a challenge because of the time and effort involved in translational research.

XI. OVERVIEW: PHASE 0 TRIALS—DR. JAMES DOROSHOW

Most oncology drugs fail in late stages of drug development, and late failure leads to enormous risk to the patient. Dr. Doroshow presented an overview of Phase 0 Trials to show how earlier testing can lead to better understanding of the molecular mechanisms of action and decrease late-stage failure rates in oncology drugs. He reasoned that as technological models have changed over the past 30–35 years, the

research community should keep pace by altering their models of trial designs. Clinical studies begin with Phase I trials to identify the maximum tolerable dosage to humans, but often without developing appropriate biomarker targets and assays. Although funding is a critical issue in this preclinical to clinical transition, biomarker development is essential for successful target modulation trials and imaging trials.

Dr. Doroshow's team is very interested in conducting preclinical investigations into biomarkers and in developing PK/PD assays for qualification during the trials. The opportunity to pursue this interest began with the publication of the IND (investigational new drug application) guide to regulatory submissions. The IND provides a means for administering investigational drugs and biologics to small samples of humans prior to clinical trials (hence, the term "Phase 0" or "pre-Phase I trials). The exploratory IND allows for bioavailability studies, microdosing, and proof-of-concept validation. Phase 0 trials also provide a means for developing reliable standard operating procedures (SOPs) for tissue acquisition, handling, and processing, which can improve histological results. They involve drug biodistribution and binding, using novel imaging technologies, and innovative statistical designs. Phase 0 trials can improve the efficacy and success of subsequent trials by eliminating an agent early in clinical development because of poor PK/PD properties and by informing subsequent trials, providing a closer approximation to a safe but potentially effective starting dose and support for limited sampling. Most Phase I trials do not emphasize PD markers because they have not been developed in the preclinical setting. While Phase 0 trials offer promise for developing drugs with wide therapeutic indexes, they present unique statistical and ethical challenges and as such, require an integrated research team, which can be very costly. These ethical challenges were the topic of discussion at a Phase 0 trials symposium held at the NCI last week. The main ethical concern revolved around administering multiple doses of an exploratory drug with no guarantee of therapeutic result, which is in contrast to Phase I trials.

Dr. Doroshow presented the results of a recently completed Phase 0 trial using a compound developed by Abbott Oncology. The exploratory IND was accepted by FDA in May, the first patient was treated in June, and the study was completed in October. The objectives of the study were to inhibit poly-ADP ribose polymerase (PARP) in tumor samples and in peripheral blood mononuclear cells using a single nontoxic dose of ADT-888; determine the PKs involved, and determine the time course of inhibition. Thirteen patients received 10, 25, and 50 milligrams of ABT-888, which inhibited the target at clinically achievable concentrations in 6 of the patients at 24 hours. The results indicated that the compound would be would be much more effective when combined with DNA damaging agents, so the industry sponsor canceled plans to conduct Phase I trials with ABT-888 alone and instead moved forward in conducting combination trials. Time was saved, therefore, by determining the PK agents and developing PD assays in the preclinical stage. This example demonstrates the potential benefits of conducting Phase 0 studies: an overall decreased timeline for cancer drug development, real-time PD/PK analyses, the efficient use of resources, and more defined targets and SOPs for human tissue acquisition that work in the clinical setting.

Questions and Answers

Dr. Chabner commented that the DCTD trial information was interesting and that the general plan for early evaluation of a candidate agent or new target was commendable. He added, however, that most other trials are multiple-dose trials, so the timeline comparisons to the DCTD trial were not valid comparisons. He suggested that the company is taking a risk by accepting data on a single dose, and speculated that it might be motivated by the fact that there are other PARP inhibitors in clinical trials, so they may want to be on board with their own. Dr. Doroshow agreed that Phase 0 trials would not replace Phase I trials, but stressed that Phase 0 would provide crucial information for later phases, adding that waiting for Phase II to develop the assay or determine if the target was hit, is really too late. It is important to develop PD assays that will enhance the targeted agent up front.

Dr. Richard Pazdur, Director, Office of Oncology Drug Products, FDA, stated that industry represents an area that could be used to test hypotheses and eliminate drugs that are not going to work, so he asked if industry might be interested in pursuing Phase 0 studies. Dr. Doroshow explained that Phase 0 results first need to be published to show that they are feasible and that they are useful to people in decreasing the timeframe. Results will need to be published before industry can be expected to join the effort. Dr. Pazdur then asked if other institutions were showing interest in conducting Phase I studies. Dr. Doroshow replied that there were many academicians who would like to be able to do proof-of-concept trials, so the question is: How do we support the development of the assays that are done in the appropriate way for them to get the answers they need? Most assays now are not very informative, and tissue samples remain unutilized in the freezer.

Dr. Atala cited a recent Tufts University study showing the average time for drug approval at 14.2 years and a cost of $980 M. He asked how involved the FDA was in reducing the number of patients for these studies. Dr. Pazdur replied that the drug sponsor determined the number of patients, not FDA. Dr. Atala countered that the dialogue is actually being directed by both parties and often the FDA is mandating the number of patients. He also suggested that Phase 0 trials may be delaying drug development and adding costs if the whole approval structure is not changed to accommodate it.

Dr. Barker added her approval of Phase 0 trials, saying that early elimination of compounds can lead to much better informed Phase I trials and in the end save money and time. Dr. Pazdur concurred and a simultaneous discussion ensued between Drs. Barker, Pazdur, and Chabner regarding industry's role in conducting preclinical toxicology studies and the concern with the reliability of those studies. They also discussed the issue of monitoring tumors versus taking multiple biopsies, from a histological standpoint as well as from ethical and logistical standpoints. Dr. Chabner noted that it was difficult to find patients willing to undergo multiple biopsies with no hope of therapeutic effect.

XII. 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 IRG recommendations was affirmed by all serving Board members present. During the closed session of the meeting, a total of 1,867 applications were reviewed requesting support of $539,230,028.

TUESDAY, SEPTEMBER 18, 2007

XIII. MINI-SYMPOSIUM: FUTURE OF IMAGING IN THE NCI PROGRAMS: FROM MOLECULE TO MAN—DRS. LEE HELMAN, SRIRAM SUBRAMANIAM, THOMAS MISTELI, JAMES TATUM, AND PETER CHOYKE

Introduction. Dr. Helman introduced the mini-symposium on the future of imaging in the NCI programs. He explained that, to accomplish the CCR's mission, the NCI is working to integrate basic science, translational science, technology development, and clinical science across Centers of Excellence, and through faculties and working groups. A Center of Excellence is a place where a group of world class people come together; emerging areas of emphasis include inflammation and cancer, cancer stem cells, and metastases. All of these topics cut across the CCR's training programs.

Imaging has become a major priority of the basic science and clinical programs, and it is believed that the distinction between imaging and pathology will begin to blur. Novel imaging approaches will help in basic discovery research, translational applications, and non-invasive patient care. Functional imaging may even assist with the determination about activation of a particular target and whether or not that target is inhibited. Significant knowledge about this, for instance, has been gained from research in pediatric leukemia. Early intervention is key, which means that early change of therapeutic modalities is important and that studies therefore need to be done in real time. It is believed that the preclinical model testing will be dependent on imaging, relying on the ability to assess target interruption in real time using novel imaging approaches.

The NCI is developing an integrated clinical oncology imaging clinic in close collaboration with the Clinical Center to allow imaging studies on clinical protocols to be conducted in a timely manner. The first phase is to develop a nuclear imaging team primarily focused on PET, SPECT, and radioimmunotherapy. Initially it will be located in the Clinical Center.

Dr. Helman next described several imaging advancements that would not be discussed by the presenters. One is oxygen tension imaging, which combines an electron magnetic spin with a nuclear spin to allow one to receive spatial information as well as oxygen tension in real time. Alterations in oxygen tension can be seen in a tumor over time. Another is the examination of a glucocorticoid receptor with GFP that was superimposed on a promoter chip and allows the identification of all the genes that are being actively turned on by engagement of this transcription factor, the glucocorticoid receptor.

Dr. Helman introduced the speakers: Drs. Sriram Subramianiam, Senior Investigator, Laboratory of Cell Biology, CCR; Thomas Misteli, Senior Investigator, Laboratory of Receptor Biology and Gene Expression, CCR; James Tatum, Acting Associate Director, CCR; and Peter Choyke, Senior Investigator, Molecular Imaging Program, CCR. Dr. Niederhuber said that the ability to move from the subcellular level to the patient is the future for drug development; new agent development and biomarker development are intimately tied together.

Towards Mapping Cellular Architecture at Molecular Resolution With 3-D Electron Microscopy. Dr. Subramaniam described CCR's work in looking at cancer cells and viruses at resolutions that were thought unprecedented as recently as several years ago. The interest in biology starting from molecules all the way to humans ranges in magnitude size from 10^1 to 10^{28} Daltons. In the history of imaging of molecules and larger items, x-ray- and magnetic resonance-based methods have achieved great success at the very small and the large ends of the spectrum. The central region, however, has largely been the realm of imaging microscopies, such as light or electron microscopy. Nevertheless, there is an extremely important and fundamental gap in imaging, primarily roughly centered in the size

range of objects that have sizes on the order of 100 to 200 nanometers. There are many processes that occur at the subcellular level that the scientific community would like to understand, but the methods to do this have not been developed. An example of this is a movie of a neutrophil chasing a bacterium on a plate of reglA cells and eventually engulfing the bacterium; at the molecular level, which is not shown in the movie, there are hundreds of genes that are changing their levels of expression and many proteins being rearranged. The intent is to understand dynamic processes like this by using developed and applied tools of high resolution looking at atomic structures. The methods currently used in the laboratory are referred to as "3-dimensional (3-D) electron microscopy."

The CCR's general philosophy about imaging is based on electron tomography. Electron microscopes provide projection images of objects much like an x-ray machine does; however, by recording the specimen relative to the electron beam, similar to the CT scan, a large number of projection images can be collected and computationally combined to make tomograms of small molecules, viruses, and cells. They provide an extraordinarily rich amount of information on the organization of the molecules within these entities. Dr. Subramaniam next presented four examples of the CCR's imaging work and concluded with future challenges and opportunities for subcellular imaging.

(1) Architecture of dynamic molecular machines. Dr. Subramaniam described imaging of the whole cell through the multiprotein complex, which is a dynamic protein complex that is critical for the synthesis of acetyl co-enzyme A; this is approximately 15 nanometers in size. Imaging of the pyruvate dehydrogenase complex has been used, for instance, to understand the relationships between different proteins that exist in the mitochondrial space and to understand at a molecular level how they go about the business of metabolism. Images of single, multi-enzyme complexes have been compiled in the laboratory, and thousands of images have been averaged to reconstruct 3-D structures and atomic interpretation. Using much higher resolutions has enabled researchers to incorporate the density map to look at individual helices, which is x-ray crystallography, thus aiding in the understanding of how specific molecules are assembled together. This work is moving toward a greater functional understanding. After nearly 4 decades of pyruvate dehydrogenase structure studies and biochemical studies, much has been learned about the architecture of the whole complex, such as gaps, moving parts, swinging arms, and active sites.

A different approach has been used to study problems associated with bacteria, particularly the complexity of bacteria in motion, shown through an example of chemotaxis of mammalian cells. Imaging tools have captured the spatial architecture of chemotaxis signaling assemblies; in many respects, this collection of proteins functions like an analog computer. There are about 1 dozen proteins, and researchers have conducted GFP labeling studies of individual components. Research that recently was published showed that electron tomographic approaches could be used to image intact cells, the beginnings of the chemotaxis apparatus and the individual receptor clusters that sit at the cells; tomography has been used to image in 3-D receptors in cells, which basically allows snapshots of the spatial architecture of signal transduction. Current research that is not yet published has been conducted in cells beginning to reconstitute signaling assemblies that have been genetically engineered to completely lack all components of the chemotaxis apparatus (i.e., *Che*$^{-}$ *E. coli* cells). Components are added back systematically; the power of averaging allows the movement from images to average structures of receptors.

(2) HIV molecular structure and entry mechanisms. Current work on HIV is beginning to provide insights into the structural variation of the enveloped glycoproteins on HIV and related viruses and has led to some surprising and new discoveries on the nature of viral entry into CD4 positive T cells. Immunodeficiency viruses like HIV and SIV are very complex; they are not symmetric and each individual virus is different from the others. Obtaining structures of these viruses has been a confounding

problem in structural biology for a long time and is particularly acute in the case of HIV because the surface glycoproteins are probably not affected. They have different conformations and have proved resistant to being crystallized in the chimeric form. Tomographic approaches have been used to computationally box out the individual volume corresponding to each one of these envelop glycoprotein trimers and begin to average them to make 3-D maps at resolutions approaching 20 angstroms, which provides an increasingly better view of the surface glycoprotein structure. The implications of this work to vaccine design are profound in that this may be the first direct determination with validation of the trimeric structure and may lead to a number of efforts to develop a rational vaccine design.

Another aspect is the nature of antibody neutralization of these viruses. Tomography has shown that some of the most potent neutralizing antibodies, a polyvalent CD4 construct, in fact neutralize HIV by cross-linking virus types, both in neighboring viruses and in the same virus. It also has revealed a significant increase in the probability of viral rupture by adding these antibodies. The structure essentially opened the doors to the synthesis of more effective therapeutic agents, an idea that will be pursued in the years to come.

A final example of CCR's work with HIV, which was published in 2007, is the discovery of the HIV entry claw, a very distinctive structure that is reproducibly formed between HIV, SIV, and CD4 positive T cells. It has about six spikes that contact the T cell. The CCR is actively working to define the claw's composition, its origin, why the spikes fall off when the claw is formed, and other structural questions that imaging studies and higher imagery resolution have raised.

(3) Spatial mapping of signaling transduction. A different approach is the development and use of tools to image signaling assembly for intact cells—essentially whole cells are frozen to be very close to the physiological shape. The idea of imaging receptors or receptor assemblies in intact cells is exciting both from the imaging perspective and from the point of view of being able to create a computational model and understand how the dynamics lead to signal transduction *in vivo* in a real cell. Earlier work used an approach called transcriptional electron microscopy, in which one looks through cells; large, mammalian cells and tissues could not be easily looked through, however, because of their thickness. In an industrial partnership with a company, the NCI developed and applied a technology that had been used by the semiconductor industry for cutting into silicon chips. This technology investigates the interior cells using a dual-beam electron microscope, through which a focused ion beam ablates away small portions of the surface of a cell, a picture is taken, and a 3-D volume of the cell is built through reiterations of the process. This process was used with yeast cells beginning with a cross-sectional view of a cell, and Dr. Subramaniam noted that the laboratory was able to reach a 200 nanometer reconstruction of a dividing yeast cell. Information about this process was published in July 2006.

(4) Probing subcellular signatures of mechanisms. New methods have been developed to image large mammalian cells and extract information that might be clinically useful to understand the progression of disease in a relatively short time. For example, for the first time, human melanoma cells can be imaged with extremely high resolution. Technology has been used to interrogate the interior of a melanoma cell and melanocytes, with the aim of uncovering the distribution of melanosomes and speed the process of characterization of different stages. Dr. Subramaniam shared examples of the image quality now attainable, including the best resolution in 3-D of mammalian cell imaging that he had seen. A picture is taken with a scanning electron microscope of a single slice of a cell in which the mitochondrial and two membranes are visible. From these images, 3-D volumes of whole cells are built. In the case of a whole melanoma cell, one can begin to visualize the 3-D architecture of mitochondria, the relationship to endoplasmic reticulum, and essentially the entire complement of organelles in the cell. This is exciting from a computational point of view because it allows, for the first time, the development of reasonable models for the spatial architecture of different components in the cell. Information coming

from imagery includes very large datasets on the spatial architecture of mitochondria, the endoplasmic reticulum in 2-D and a slice in 3-D; it is hoped that cataloguing the shape changes and differences between normal and cancer cells will yield knowledge about how cells at different stages might have different morphologies within the cell itself.

Dr. Subramaniam described future challenges and opportunities for subcellular imaging. Technological investments may have significant impact in terms of automating the process and making it broadly applicable to other systems. Regarding automation, the CCR has initiated a partnership with a private company to integrate many of the individual steps in producing a 3-D structure. The instrument called the Titan Krios that will help accomplish this will arrive at the NCI soon; it will be the first of its kind in the United States. Its applications to nanoparticle characterization also may be very important. In addition, the compositional mapping of a cell can provide a rich database of information that could be useful for other research fields. Researchers can routinely move from two to three dimensions, and now they can localize individual nanoparticles that can be gold-labeled antibodies; with the imaging technology, they also can combine 3-D imaging with the ability to specifically localize proteins using antibodies and gold-derivatized secondary antibodies. The NCI is exploring partnerships with the NIST and other agencies to incorporate mass spectrometry in the characterization of the protein composition in interior cells. Dr. Subramaniam said that an important goal in cellular biology is to define in 3-D the proteins that comprise these cells.

Frontiers in Cellular Cancer Imaging. Dr. Misteli described frontiers in cellular cancer imaging, including the goals and current status of cellular imaging, current technologies, and the future of the field. Goals of cellular imaging are to impact basic discovery through the visualization of intracellular structures and processes, the placement of cellular mechanisms into a spatial and temporal context, a probe of the contribution of spatial and temporal organization to function, and the discovery of novel cellular and molecular mechanisms. Research in cellular imaging aims to impact applications by probing disease mechanisms *in vivo*, developing diagnostic tools based on morphological properties, and strengthening drug discovery and testing.

There have been a number of quantum leaps in imaging. The visualization of virtually any cellular component, for example, is now possible due to a strong probe development that allows the localization of proteins, DNA, RNA, and lipids. Much of this work can be performed inside living cells. Molecular interactions can be seen *in vivo*, as well as complexes and where particular complexes form inside of cells. Another quantum leap is the ability to image beyond the resolution limit; physicists have broken the resolution limit to approximately 50 to 75 nanometers.

Dr. Misteli next described the most important imaging technologies in terms of the impact on cancer biology: lifestyle imaging, genome imaging, and high-throughput imaging.

Lifestyle imaging focuses on how biology actually works. There has been a green revolution in imaging that has allowed the imaging in living cells. This revolution is based on a small protein called the green fluorescent protein from a jellyfish, and this protein can be fused to any other protein of interest and can be expressed in cells. Because it is fluorescent, it can be seen inside living cells and thus allows researchers to look at, for instance, the dynamics of proteins. Examples of this include Dr. Gordon Hager's (CCR) work on the nuclear import of the steroid receptor, and the metastatic cell migration in a tumor. Another approach is the visualization of dynamics by photobleaching, which removes fluorescence; the return of the fluorescent signal over time reveals how quickly proteins and other cellular components move around. This process has been extended to specific genes, including a ribosomal gene, thus visualizing the recruitment of transcription factors to genes inside living cells. Dr. Misteli showed an example of this with a method that looks at the PTEN tumor suppressor; using photobleaching methods,

his laboratory measured the import rate of these proteins of the wild-type protein and found that the mutant protein is less efficiently imported. The assay showed that this occurs because of post-translational modification into degradation of the protein in the cytoplasm. This work on the molecular mechanism has inspired the search for novel therapeutic approaches for particular patients. DNA and RNA also can be visualized in living cells, using specific sequences either from a bacteria or a phage. One can then use a specific binding protein to this sequence, which does not exist in mammalian cells, fuse to the green fluorescent protein again, and visualize either the DNA or the RNA in living cells. Dr. Misteli also described other research that involved an experimental system to visualize broken chromosomes in living cells. Opportunities in live-cell imaging include work in multi-probe imaging; the imaging of molecular interactions; and the imaging of cellular processes, such as enzymatic events and modification. Research also is needed in long-term observations and high-resolution tissue and animal imaging.

Another technology is focused on imaging the genome. The genome has been imaged over many years using fluorescent *in situ* hybridization, in which one identifies meta-phase chromosomes to find chromosomal translocations and chromosomal aberrations. Some of the most recent and exciting work has come from performing *in situ* hybridization on the interface cell nucleus—that is, the interface genome. It has revealed that the genome inside of the cell nucleus is non-randomly organized so that different chromosomes and single genes appear to be located in different places. These positioning patterns are cell-type specific, tissue specific, and evolutionarily conserved, and they change during differentiation development. This is relevant for physiology and important for cancer because regions in the genome that undergo frequent translocations, such as human lymphocytes myc and IgH that form translocations to give Burkitt's lymphoma, are generally in close spatial proximity. In short, they are predisposed to undergoing translocations. One of the interesting aspects of the gene positioning patterns is that the position of a gene often changes before the activity of the gene changes. This suggested the idea of using this positioning information for diagnostic purposes—that is, perhaps a gene in a normal cell is positioned differently from the same gene in the malignant or even in a premalignant cell and this information could be used to distinguish normal versus malignant cells to pick up metastatic or even premalignant cells. This idea has been tested in breast structures through a 3-D cell culture system. Of 11 genes that were tested, 4 were found to be localized differentially between normal and cancer cells. This study has been extended to actual tissue sections and the same behavior has been witnessed; the cancer samples that have been used are extremely heterogeneous. This new diagnostic application offers advantages of early detection and very small samples (i.e., 200 cells). Moreover, it does not require mitotic chromosomes, can be applied to solid tumors, and allows an analysis of subpopulations. Another advantage is that probes to all genome regions are available. Frontiers in the genome imaging area include the further development of diagnostic applications and the systematic mapping of the spatial organization of the entire genome.

High-throughput imaging is a promising technology that focuses on the systematic and unbiased exploration of biological patterns. This approach contains two components: imaging and computation. The imaging component uses automated sample preparation of a large number of samples and fully automated microscopy to obtain a large number of images. The computation element involves image analysis and measurement, as well as data exploration and statistical analysis, to find particular patterns or analyze images in an unbiased way and discover new patterns. High-throughput imaging can be used to look at growth patterns, intensity, shape, and localization of either genes or proteins. In addition to the discovery of new patterns, this imaging technology can be used for screening purposes. The process is to select a known biological pattern, such as the localization of a protein that is different in cancer and normal cells, perform either RNAi or small molecule library screens, and identify factors that affect these patterns. These changes will be detected by automated imaging and any indicator can be examined. Through these screens, researchers can obtain new molecular mechanisms in an unbiased fashion using

RNAi libraries. Drug discovery can be accomplished with the help of small molecule libraries, and this can be applied to diagnostic applications that target gene positioning patterns, protein localization patterns, and morphological markers. One ongoing screen that is being conducted in collaboration with the NIH Chemical Genomics Center, for example, looked at the ratio of a GFP and a red fluorescent protein inside cells; more than 100,000 compounds were involved in this screen, with seven concentrations per compound. It was conducted in a 1536 well format. The screen took approximately 8 days, and the data analysis took 2 to 3 weeks; follow-up is expected to last for several years. The studies using high-throughput imaging are an example of NCI's ability to develop assays that pharmaceutical companies would not develop. The most difficult part for imagery is the hardware, the equipment, and the image analysis.

Technologies and research that will be important in cellular imaging and for cancer biology include: increased spatial resolution; the combination with computational approaches (e.g., image analysis, pattern recognition, and kinetic modeling); multi-probe imaging; and additional work in high-throughput imaging. To enable breakthroughs in imaging, resources must be provided for technology development and support made available for high-risk projects. Long-term support is needed beyond conventional R01 grants, including support of interdisciplinary technology development. Finally, technology dissemination should be facilitated. Cellular imaging will have a major impact on cancer biology, and the NCI is well positioned to take advantage of this because of its strong basic science and translational components.

Developing Novel Imaging Biomarkers for Monitoring Cancer Treatment. Drs. Tatum and Choyke presented information about defining novel imaging agents. Dr. Tatum explained that he would define imaging, discuss its power and its significance to cancer, and then describe challenges. Imaging is the ability to detect and measure one or more properties of interest in a spatially defined sample. An example of this is the use of proton MR spectroscopy in breast cancer by Dr. M. Garwood at the MR Research Center at the University of Minnesota, which shows a mass that is easily discriminated and thus has been spatially defined. Proton spectroscopy also has been used to show response to chemotherapy, as well as changes in mass size, spectra, and ratios in studies of invasive ductal carcinoma. Most imaging techniques are non- or minimally invasive and non-destructive and either do not perturb a system or do so in a predictable manner. They can provide dynamic real-time data, repeated measures and integrative or systems data. Imaging is the ultimate methodology for understanding complex systems biology. The most complex of such systems are tumor biology and physiology.

MR spectroscopy is used successfully, but challenges remain in imaging many things involving cancer, such as molecular signatures. For this reason, an imaging probe is used to spatially define and measure molecular constructs that interact with a target and provide enhanced *in vivo* detection by co-localization of one or more beacons. This has been seen in work from Munich using the cyclic peptide galacto-RGD to look at binding with the alpha-V-beta-3 and probably beta-5 as well. Dr. Tatum shared an example of a total body PET scan that included a lymph node from a positive melanoma tumor; he then showed it as revealed by the CT scan and the combination of the scans. This work could not be completed with MR technology or any other current clinically diffuse techniques. A challenge remains in that the only PET probe currently approved and distributed commercially is FDG, although there are many probes being developed and some are rapidly translating through the imaging drug development pipeline.

One of the tasks at hand is to find gaps in the pipeline, particularly for translational research, and determine whether the gap could be bridged. Most of the NCI's probes come from extramural investigators funded through extramural grants. A robust platform of agents is being developed: approximately 80 CIP grants are funded to support the discovery, development, and application of

molecular agents; 125 unique agents are in various stages of development; and an extensive number of receptors and targets are being worked on by extramural investigators. Moreover, collaboration is occurring between extramural and intramural investigators. To resolve the problems posed by drug development research, the Imaging Drug Group has been created to look at the available resources for the steps involved in the development of imaging drugs, from discovering agents through the conduct of clinical trials. Many of the agents in the pipeline are PET agents and there are some MR agents. Dr. Tatum said that one interesting molecule is a fluorinated synthetic L leucine analog, called FACBC, which looks at the L amino acid transport system. It is being studied by Dr. Mark Goodman at Emory University with NIH funding. Initial preclinical studies in the prostate model reveal terrible activity in the bladder, but the FACBC does not include much bladder activity and has good uptake in prostate cancer. The agent was submitted to NCI's DCIDE program, underwent internal and external reviews, and successfully became an IND. A Phase I trial began, and there have been two R01 amplifications for glioma and prostate. The agent now is pipeline to become an NDA-type of application for a very new novel agent. Dr. Tatum also described several studies of FACBC involving glioma, bilateral prostate, and a sextant biopsy predicted bilateral prostate cancer.

The last phase planned for novel imaging drugs is to begin Phase 0 and 1 trials. One nanotechnology agent, for instance, is being targeted by several large trials. This has involved strong associations with the Nanotech Alliance, particularly the NCL and other nanotech centers, which is important because most of the imaging probes under development likely will be nano-based and imaging is very important to the development of nanotechnology. Dr. Tatum referred to research about advances using nanotechnology that was published in *Nature* (January 2007, Vol. 2).

Imaging roles in oncology include understanding human tumor biology through novel probes and nanotechnology; drug and therapy development through validated imaging probes for clinical use and Phase 0 trials using imaging probes; and clinical decision making, including diagnosis and staging, therapy selection (whether stratified or personalized), and therapy monitoring. Dr. Tatum said that probes are not the only technology to produce high-resolution imagery; he showed a high-resolution ultrasound resulting from the Visual Sonics machine and noted that work is underway to develop molecular probes that can be used for ultrasound.

Dr. Choyke said that the Molecular Imaging Program was formed at the NCI in 2004. Imaging biomarkers provide more rapid assessment of tumor response and are superior to invasive biopsy from a variety of points of view in clinical trials, including ethics, sampling errors, reproducibility of results, and patients' acceptance of all that is involved. They are, however, expensive to develop, and they present a difficult IND process. Additionally, the pharmaceutical industry is less interested in diagnostics, and imaging and probe development has become a "cottage industry" that is plagued with a lack of standardization in terms of formulation and imaging protocols.

NCI's Molecular Imaging Program involves a multidisciplinary team composed of chemists, molecular and cellular biologists, and imaging physicists and specialists. The Program is one part of NCI's imaging drug development organization, the Joint Development Committee, which serves as the interface between the extramural and the intramural worlds. Another part, the Imaging Drug Group, is working with more than 125 new compounds; some of those compounds can be brought to the intramural program via this Joint Development Committee. Agents also are being developed intramurally through the Nanotechnology Characterization Laboratory through efforts at FDRDC's Small Animal Imaging section, and the Molecular Imaging Program is working closely with the Experimental Therapeutics Group to bring in and test new agents through the Phase 0 or exploratory IND mechanism. Dr. Choyke next described specific projects that have been brought to the clinic in varying steps, including

radiolabeled antibodies, the development of macromolecular MR agents as surrogate markers for therapy, and a variety of PET agents.

Radiolabeled antibodies: ^{111}Indium Trastuzumab (Herceptin). Indium trastuzumab or herceptin (HER2/neu) was selected because of its wide use in the clinic today. It is expressed in many tumor types, particularly in breast cancer, where it is useful as a monotherapy against breast cancer. A "herceptin scan" would be able to identify disease with a potential of quantifying HER2/neu expression *in vivo*, monitor disease response, provide dosimetry for radioimmunotherapy, and provide a basic molecular platform with the same conjugate labeled with an alpha or beta emitter. A key component has been Dr. Martin Brechbiel's work on a bifunctional chelate that binds to the monoclonal without changing its function or binding characteristics. The chelate attaches the radionuclide to the nonfunctional part of the monoclonal (i.e., the Fc portion of the antibody), thus not influencing its function. The IP for this work is owned by DHHS, which allows the NCI to combine the research with a variety of different kinds of monoclonal antibodies without incurring multiple IP issues. This also has been explored in mouse models of disease, including labeling the same agent with indium for imaging but also Y90 and Y86 for beta emission and PET imaging (respectively, lutetium 177, which is a beta gamma emitter, and bismuth 213, which is a highly toxic alpha emitter), and using this as a potential means of carrying therapy to cancer. Preliminary work has shown that this technique allows imagery; Dr. Choyke showed examples of a lung metastasis in a 54-year-old female with metastatic breast cancer and a liver metastasis in a 67-year-old female with metastatic breast cancer. There are a number of other monoclonals and work in antibodies that are in the development pipeline as well.

Macromolecular Contrast Agents: Gadolinium-Albumin. The rationale for this agent is that glioblastomas have high mortality, and convective enhanced delivery is at least one method of introducing high concentrations of drug into the tumor bypassing the normal blood-brain barrier. Most macromolecular drugs, however, are administered blindly unless they are mixed with an agent that has similar convective properties. Consequently, one agent has been designed that matches the convective properties of at least one of the convective agents, gadolinium albumin, which is considered a surrogate marker. It has more than 20 gadolinium atoms per albumin and accurately depicts drug delivery on a real-time MRI. The protocol will involve 20 patients with glioblastoma. The agent currently will be a pegylated IL-13 with gadolinium-albumin co-infusion in the Clinical Center's intraoperative magnet, and additional catheters are being produced as needed to treat the tumor. Sequential infusions also may be involved. The pipeline for this agent includes preclinical testing of Gd-G8-Dendrimer-iv and a number of other nanoparticles.

Novel PET Agents for Therapy Monitoring. FDG-PET is distributed worldwide by a network of commercial providers. Novel PET agents, however, are synthesized in local laboratories with no distribution system. Individual synthesis boxes at different sites lead to variable products. The recognized solution for this is to use commercial providers to manufacture novel PET agents and distribute them for clinical trials. One of the agents that is furthest along is ^{18}F-L-Thymidine (FLT). FDG is nonspecific for cancer. FLT was based on the drug AZT; it shows correlation with specific markers of cell proliferation and thus has the possibility of being much more specific for cancer, although potentially less sensitive, than FDG. Projects underway that involve FLT are looking at recurrent lymphoma, medulloblastoma, and glioblastoma multiforme. Breast cancer metastases to brain and anti-TGF-β antibody therapy projects are under consideration. Dr. Choyke also described work on α-V-β-5 integrin, which is a target for angiogenesis—and a popular target; an F18 agent was utilized in a Phase I trial and a normal, healthy volunteer demonstrated a blush early on after injection that proved to be a low-grade glioma, thus illustrating the power of this agent for detecting angiogenic tumors. Moreover, images of PET in patients with metastatic breast cancer show the uptake of this agent corresponding to the CT scan. This appears to be a promising marker for angiogenesis and may be a marker for angiogenic

response to inhibitors. In addition to FLT, other agents in the pipeline include the RGD agent for angiogenesis, MISO for hypoxia, and C11 acetate for prostate imaging.

Dr. Choyke said that there is both great potential and multiple challenges in the development of novel imaging biomarkers. He reiterated that NCI's Molecular Imaging Program, along with the whole Joint Development Committee, acts as a test bed for new imaging agents by: addressing barriers of production; determining the value in small pilot trials; standardizing imaging protocols and production; offering the potential for commercialization; and improving the efficiency of large, multicenter trials.

Questions and Answers

Ms. Giusti asked about opportunities for collaboration, such as between the NCI and foundations, on disease-specific grants. Dr. Misteli said that opportunities exist and, for example, some of the research that he had presented is supported by the Progeria Research Foundation. He indicated that IP rights need to be considered and negotiated, however, with each foundation. Dr. Niederhuber added that the Clinical Center is where the NCI works on unusual and rare diseases, such as myeloma.

Dr. Chabner noted that the labeling of drugs and small molecules is a problem in imaging and asked about plans to perform this systematically. The response was that the NIH is putting forward an initiative to build a PET facility that will include a research facility; it will be important to remain very cognizant of labeling drugs as many of them will be C11 and short half-life. In addition to FLT, which is available for commercial trials through three vendors, F-MISO is available as an agent to pharmaceutical companies. Other agents are moving ahead in the pipeline, including FES. Dr. Helman said that much work is being conducted in parallel, and compounds are more likely to be selected if they support, for instance, work in imaging and biopsy biomarkers.

Dr. Coffey stated that the presentations provided stunning displays of NCI's support of cellular, genomic, and chromosome biology. He encouraged the NCI to remain at the cutting edge and not dilute the studies with a plethora of additional samples; he referred to prostate research that indicates changes have occurred to those areas that will develop cancer before the cancer develops. Dr. Misteli added that this same phenomenon has been seen in breast samples.

Dr. Atala described the work as fantastic and exciting, and he asked how the NCI will continue to bring work on the nanometer gap into the *in vivo* setting. He also encouraged the NCI to bring bioinformatics into the effort to make sure that the data needed are available. Dr. Subramaniam agreed and said that the examples he presented have been focused on moving toward *in vivo* studies. Dr. Misteli noted the important role of computer scientists in the studies, as well as hardware issues related to technologies, such as high-throughput imaging.

Dr. Barker echoed Dr. Coffey's belief that many of the breakthroughs will involve genomics; the biophysics of this in 3-D space likely will be one of the most important things that can be learned during the next decade. For this reason, the NCI now is working to bring the physics, chemistry, and computational sciences into the equation. She also noted the difficulties posed by many small laboratories operating independently in imaging and drug development and stated that the Interagency Oncology Task Force is working to create a critical path for agents.

Dr. Kenneth Cowan, Director, UNMC Eppley Cancer Center, and Director, Eppley Institute for Research in Cancer, University of Nebraska Medical Center, said that these imaging technologies—which will lead to exciting changes at the molecular and cellular levels and networks (i.e., systems biology)—are expensive and likely will change every 2 years; to prepare for and make the most of this, the NIH

infrastructure should downsize to the point where the patient throughput for routine imaging is less and experimental imaging is greater. Drs. Helman and Niederhuber agreed, and Dr. Niederhuber mentioned the NCI's computational center and state-of-the-art small animal imaging facility at the FDRDC.

Dr. Chabner suggested that the NCI intramural medical oncology program should probably be oriented to conducting very specific, high technology, innovative translational trials involving imaging and molecular oncology that are not easy for academia to do. It also could focus on recruiting post-fellowship researchers who are interested in drug development studies.

XIV. STATUS REPORT: INTEGRATING THE RECOMMENDATIONS OF THE CLINICAL TRIALS WORKING GROUP AND THE TRANSLATIONAL RESEARCH WORKING GROUP—DR. ERNEST T. HAWK

Dr. Ernest Hawk, Director, Office of Centers, Training and Resources (OCTR), presented an update on the work completed in integrating the recommendations of the TRWG in collaboration with the CTWG. He reminded the members that 62 people participated in the TRWG and that they were organized into six project groups that produced 15 recommendations in the areas of coordinated management, tailored funding programs focused on translational science, and operational effectiveness. Dr. Hawk next briefly reviewed the recommended initiatives under each of these areas. He said that the NCI has worked to transform the 15 initiatives into 6 activities that will integrate very closely with the ongoing efforts of CTWG implementation. These activities are: integrating NCI management; establishing a refined translational research coding system; implementing STRAP awards; modifying/coordinating translational research awards; establishing a project management system; and coordinating activities with external constituents (e.g., foundations and advocates).

The **integration of NCI management** will be vested in the Center of Coordinated Clinical Trials (CCCT), under the direction of Dr. Sheila A. Prindiville, Director, CCCT, and Dr. Doroshow. A recruitment of four professional staff is underway, and a 12-month detailee or IPA is expected to manage startup activities. A Translational Research Operations Committee (TROC) is planned to begin operations in January 2008 to oversee and coordinate the translational research portfolio and serve as an internal oversight body of all proposed activities. The CTAC is expected to have its mission expanded to consider translational science, and perhaps its membership extended as well; this may occur in March 2008.

The **translational research award coding** provides an essential foundation to identify and manage the translation research portfolio and decisions. The coding methodology would be led by RAEB/CCCT, with input received from program staff and extramural TRWG members as needed. The coding is expected to be implemented by the RAEB for FY 2009 awards. The proposed TRWG budget includes new RAEB staff to handle the coding effort.

Regarding the **Special Translational Research Acceleration Project (STRAP) implementation**, which is a process that builds on a whole infrastructure for the oversight and prioritization of opportunities, the first round of prioritization is scheduled for July 2008 and would be led by a working group of CTAC. Based on this first set of priorities, RFAs might be released October 2009, with an award target date of July 2010. The intent is to fund development projects that are focused, closely managed, and collaborative.

Dr. Hawk described four activities addressing the **modification and coordination of translational research awards**. One is the guidelines modification of the award mechanisms, which is slated to begin in early 2008; this is essential to create incentives to progress translational efforts further

toward patient benefit. Another part of this initiative is the analysis of core services, which is expected to start in mid 2008. In addition, the integration of projects that are funding early stages of translational research—including SPORES, P01, STRAP mechanisms—with preclinical development resources, such as RAID and RAPID, is expected to begin in late 2008. Finally, the development of improved approaches for translational research training would be initiated in early 2009.

The success of the **project management system** depends on three factors: (1) the accurate identification of translational research awards through new codes, (2) guidelines modifications to reward milestone-driven progress, and (3) analysis of existing core services and other resources. The implementation of this initiative has been delayed until 2009 in the current schema to permit all those activities.

External coordination is the interaction of the NCI with outside bodies. Activity thus far includes a plan for foundation advocacy group outreach on translational research issues, specifically involving the SPORE program, in October 2007. This is being led by the Office of Liaison Activities in association with a new DCLG working group. In addition, TRWG initiatives involving industry collaboration under the auspices of the existing CTAC Public-Private Partnership Subcommittee are planned for implementation in 2008.

Dr. Hawk said that the requested FY 2008 budget for TRWG implementation is $1.5 M. Most of these expenses are focused on establishing the infrastructure to do the TRWG recommendations. He also shared the envisioned timeline for the activities that he had described earlier and noted that the timeline includes the evaluation process that will be designed in the near term.

Issues that currently are being discussed include: the accelerated implementation of a STRAP-like mechanism to fuel the most compelling translational advances (i.e., pilot testing); the facilitation of relationships with foundations and advocacy organizations in a new way (i.e., a higher level, more frequent, and more systematic); and a greater interaction between intra- and extramural programs focused on translational progress.

Questions and Answers

Dr. Niederhuber said that it would be helpful for the NCI if members provided feedback on the implementation, timeline, and proposed activities.

Dr. Everson asked about the interactions planned within the community setting, such as hospital or clinic outpatient services, because 90 percent of the cancer patients in the United States receive treatment in these settings. Dr. Niederhuber and Hawk said that this is the focus of the new NCCCP program, which did not exist when the TRWG recommendations were being developed. The NCCCP program is asking research questions, including many of them that are behavioral in nature, about how to bring translation into the community setting.

Ms. Giusti said that it would be helpful to know what NCI's priorities are among the disease groups and to know how to put collaborative grants together in such a way that the process is not slowed down by bureaucratic procedures. Dr. Niederhuber said that the NCI does not wish to slow down anyone or any process; he stressed that the NCI could serve as the common ground, connector, enabler, and facilitator among industry, private sector, academia, and other stakeholders. He added that the NCI is working to bring more cancer members onto the board of the Foundation of the NIH (FNIH) and to obtain approval from that board to create a cell or office within the FNIH that is focused specifically on cancer. Dr. Niederhuber said that an important effort underway is to re-educate CEOs of major companies so that

they know they can move money to research through the FNIH, and that there have been successful interactions with the Avon Foundation and other foundations.

Dr. Coffey noted the problem of many research groups, including the NCI, ASCO, and AACR, who appear to be seeking funds from the same donors. Ms. Giusti said that it is important to seek donors who currently are not contributing to cancer research. Dr. Chabner expressed concern about the R01 pool of funds, noting the role of the Cancer Centers in translating research from basic science to patients. Dr. Atala echoed Dr. Chabner's concerns and asked how the NCI can fund high-cost translation studies without impacting the R01 budget. Dr. Niederhuber agreed that the Cancer Centers, the SPORE program, and the STRAP program should serve as major vehicles of translation and early phase drug development. He also added that the NCI has worked hard to protect the RPG segment of its budget while working under NIH-wide restrictions.

Dr. Runowicz said that the NCAB would recommend moving the timeline back and that it would like to continue to be updated regarding progress. Additionally, the NCAB has a Subcommittee regarding the Cancer Centers and she will coordinate with Drs. Gray and Chabner about moving the Subcommittee's work forward.

XV. SUBCOMMITTEE REPORTS— DR. CAROLYN D. RUNOWICZ

Dr. Runowicz referred members to their notebooks for the minutes from the Subcommittee on Experimental Therapeutics, which was in June 2007. She said that the Activities and Agenda Subcommittee met and suggested several agenda items for the NCAB meeting. NCAB members were encouraged to provide input on agenda items that would help make the NCAB more proactive and advisory and were asked to send comments and suggestions to Drs. Runowicz and Gray.

Questions and Answers

Dr. Niederhuber thanked the NCAB for their work. He reminded the Board that he had served on the NCAB and understands the issues they wrestle with from their position. He said that a number of difficult issues that need to be addressed have been presented overtly or indirectly during the meeting, including recruitment, retention, and ethical considerations. Dr. Coffey stated that he was impressed with the meeting's presentations. He also said that reducing the funding for grants each year will have serious effects; a major problem could be the difference between the delivery of medical care and medical research. NCAB members individually could promote grassroot efforts to support NCI funding of cancer research.

XVI. ONGOING AND NEW BUSINESS—DR. CAROLYN D. RUNOWICZ

Tobacco Resolution. Dr. Runowicz said that a copy of the NCAB's Tobacco Resolution is included in the embers' notebooks. Currently, it is awaiting signature by the Secretary of the DHHS. Upon his signature, it will be sent to the President of the United States.

Followup to NCAB Site Visit at FDRDC. Dr. Runowicz noted that anyone who raised questions at the FDRDC should have received responses independently. Members who have not received answers should inform Dr. Gray and they will be resent.

Review of the Scientific Director of the Division of Cancer Genetics and Epidemiology. A working group of the NCAB was established during summer 2007 to review the performance of the Scientific Director of the Division of Cancer Genetics and Epidemiology, Dr. Joseph Fraumeni. The

review is mandatory, must be conducted by a working group of the NCAB, and must be completed within 6 months. The working group chair is Dr. John Potter, and members include: Drs. Reimer, Calle, Rebbeck, Cowan, Ramirez, and Olapade; the Executive Secretary is Ms. Kathleen Schlom.

XVII. FUTURE AGENDA ITEMS—MEMBERS

Dr. Runowicz referred members to the handout of potential agenda items. She explained that the disparity report was scheduled for presentation but was postponed because of a schedule conflict; it will be rescheduled. Other topics include Research Categorization: Disease Coding Overview; Enhancing Peer Review; and Our Investment on Cancer Research; and the NCCCP, including the organizations involved and the process of selection. Members were asked to submit further agenda items to Drs. Runowicz and Gray.

XVIII. ADJOURNMENT—DR. CAROLYN D. RUNOWICZ

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

There being no further business, the 143rd regular meeting of the NCAB was adjourned at 11:05 a.m. on Tuesday, September 18, 2007.

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

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