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NATIONAL CANCER INSTITUTE
145th NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
February 5–6, 2008

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

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
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The National Cancer Advisory Board (NCAB) convened for its 145th regular meeting on 5 February 2008, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, 5 February 2008, from 8:00 a.m. to 3:45 p.m., and Wednesday, February 6, 2008, from 8:30 a.m. to 11:30 a.m., and closed to the public from Tuesday, 5 February 2008, 3:45 p.m. to 5:00 p.m. The NCAB Chair, Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, Farmington, CT, presided during both the open and closed sessions.

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

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

Members, Executive Committee, National Cancer Institute, NIH

Dr. John Niederhuber, Director, National Cancer Institute
Dr. Anna Barker, Deputy Director for Advanced Technology and Strategic Partnership
Dr. Kenneth Buetow, Associate Director, Center for Bioinformatics and Information Technology
Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences
Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Paulette S. Gray, Director, Division of Extramural Activities
Dr. Peter Greenwald, Director, Division of Cancer Prevention
Dr. Lee Helman, Scientific Director for Clinical Research, Center for Clinical Research
Ms. Kathy McBrien, Administrative Resource Center Manager
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Mr. Lawrence Ray, Deputy Director for Management and Executive Officer
Dr. Craig Reynolds, Associate Director, NCI-Frederick
Dr. Dinah Singer, Director, Division of Cancer Biology
Dr. Sanya Springfield, Director, Center to Reduce Cancer Health Disparities
Dr. Jaye Viner, Acting Director, Office of Centers, Training and Resources
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
Dr. Leo Giambarresi, American Urological Association
Ms. Christy M.P. Gilmour, American Academy of Orthopaedic Surgeons
Ms. Ruth Hoffman, Candlelighters Childhood Cancer Foundation
Dr. Lovell A. Jones, Intercultural Cancer Council
Ms. Rebecca A. Kirch, American Cancer Society
Dr. Hal C. Lawrence, III, The American College of Obstetricians and Gynecologists
Dr. W. Marston Linehan, Society of Urologic Oncology
Mr. David Lofye, Lance Armstrong Foundation
Mr. Richard Martin, American Society of Therapeutic Radiology and Oncology
Ms. Margo Michaels, Education Network to Advance Cancer Clinical Trials
Ms. Christy Schmidt, American Cancer Society
Ms. Susan Silver, National Coalition for Cancer Survivorship
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Dr. Robyn Lynn Watson, American Society of Therapeutic Radiology and Oncology
COL (Ret.) James E. Williams, Jr., Intercultural Cancer Council

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TUESDAY, FEBRUARY 5, 2008

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF 27 NOVEMBER 2007 MINUTES—DR. CAROLYN D. RUNOWICZ

Dr. Runowicz called to order the 145th NCAB meeting. She welcomed members of the Board, the President's Cancer Panel (PCP), *ex officio* members of the Board, liaison representatives, staff, and guests. Members of the public were welcomed and invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), National Cancer Institute (NCI), in writing and within 10 days, any comments regarding items discussed during the meeting. Dr. Runowicz reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Dr. Runowicz expressed sadness for the loss of pioneer scientist, giant in cancer research, and NCAB member, 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. The Board held a moment of silence in his memory. Dr. Runowicz said that the Board has made a contribution in memory of Dr. Folkman to the Folkman Angiogenesis Research Institute.

Dr. Runowicz acknowledged an article in *The New Yorker* that recognized the vision and leadership of NCAB member, Ms. Kathryn Giusti, CEO and Founder, Multiple Myeloma Research Foundation, Inc., in her establishment of the foundation in 1998.

Motion. A motion was made to approve the minutes of the 27 November 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 2009.

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

Dr. John Niederhuber, Director, NCI, welcomed Board members and acknowledged the great loss of Dr. Folkman to the NCI and the general cancer community.

Dr. Niederhuber described the importance of reducing the human and economic burden of cancer. Dr. Elias Zerhouni, Director, NIH, and Dr. Niederhuber recently attended a health forum held by House Speaker, Rep. Nancy Pelosi (D-CA), and House Committee leaders. The topic was the impact of the cost of health care on the national economy and the importance of investment in biomedical research as one approach to address rising health care costs. More than 47 million Americans lack health insurance and there are a nearly equal number of underinsured people. In 2007, more than 1.4 million people were diagnosed with the disease, and more than 500,000 Americans died of cancer. In 2006, $206.3 B was spent on health care costs for cancer. Data show a decline in cancer mortality for both male and female populations. Dr. Niederhuber provided examples: between 2001 and 2004, the incidence rate per year dropped 3.4 percent for female breast cancer and 2.7 percent for male colon cancer. The estimated number of cancer survivors in the United States in 2007 was nearly 12 million. The NCI's challenge is to fund biomedical research with an ongoing flat budget of $4.8 B, which represents a 12 percent loss in purchasing power since 2004 due to inflation.

NCI FY 2008 Budget. Dr. Niederhuber stated that the fiscal year (FY) 2007 operating budget was $4.97 B and the FY 2008 appropriation is approximately $4.8 B, a slight increase of $7.5 M (+0.16%). He described key categories, including NIH taps and assessments, NCI requirements (e.g., mandated salary increases), and the NCI Director's reserve. The NCI has continued to work through its budgetary process that allowed a partial restoration of the cuts that had been made to the Cancer Centers, Special Programs of Research Excellence (SPOREs), and Cooperative Groups. During this process, NCI leaders evaluated programs with the expectation of reduced or flat budgets in the future and so they planned for a 3 percent reduction for each Division, Office, and Center; they also created a pool of funds for NCI-wide mandatory increases and reallocation for specific initiatives. A careful examination of potential recoveries and redeployment of funds captured from closed projects resulted in approximately $55 M available for new initiatives, expansions, and restoration of funds for ongoing projects.

In developing its operating budget, the NCI established several policies, including the decision that there would be 1 percent inflationary adjustments on non-competing grants, an approximately 2 percent decrease from commitments of record for categorical (non-modular) grants, and no reductions to modular non-competing research project grants (RPGs). In addition, the NCI would award fewer competing RPGs than in FY 2007 (1,283, down from 1,312) while meeting the NIH-provided target for competing new investigator R01 grants, and the average cost of competing RPGs would be 3 percent above the FY 2007 level. Other policies are that: Type-2 (competing continuing) grants would receive 3 percent above current levels unless the principal investigator (PI) requested less than 3 percent or the peer review recommended a budget lower than a 3 percent increase, grants recommended for seven modules or fewer would be reduced by 13 percent, and Type-1 (new competing) grants would be cut by 17 percent from the level requested and approved by peer review. Based on these policies, it is estimated that R01 paylines will be at the 12th percentile; new investigator paylines at the 19th percentile, and very large R01s (i.e., those that request more than $700,000 in direct costs) at the 14th percentile for the first and second rounds. Other RPG projections include R21 grants at the 14th percentile, R03 at a 210 priority score, R33 at a 155 priority score, and P01 grants selected on a case-by-case basis. Dr. Niederhuber provided several examples of downsized and discontinued programs that reflect these policies.

President's Budget FY 2009. Dr. Niederhuber stated that the President's Budget (PB) for FY 2009 is $4.8 B, which includes an increase of $7 M (+0.1%) from 2008. Dr. Niederhuber referred members to copies of the FY 2009 Professional Judgment Budget included in the meeting materials.

Thoughts About the Future. Dr. Niederhuber stated that NCI's strategic objectives remain the preemption of cancer at every opportunity and the achievement of the best outcomes for all. To accomplish these goals, the NCI is working to understand the causes and mechanisms of cancer, accelerate progress in cancer prevention, improve early detection and diagnosis, and develop effective and efficient treatments. The objective is to understand the factors that influence cancer outcomes, improve the quality of cancer care, improve the quality of life (QOL) for cancer patients, and overcome cancer health disparities. Dr. Niederhuber described several ongoing and planned activities to help realize these objectives.

It is important to identify and understand the genetic defects that lead to cancer, and the NCI continues its strong support of the Human Genome Project and the HapMap to understand germline defects. The information that results from these efforts will have a significant impact on the ability to diagnose cancers, translate them into preventive measures, and facilitate studies in pharmacogenomics and the development of therapeutics, both gene therapy and novel small and large molecules and biologics. Innovation will be needed to translate the genetic information into research activities that target gene expression, defects in or absence of proteins, and the effect on cell signaling pathways or communication pathways between cells as well as tissue function and the presence or absence of disease.

Dr. Niederhuber highlighted several upcoming events. The NCI workshop on "Integrating and Leveraging the Physical Sciences to Open New Frontiers in Oncology," which will be held in late February, will explore opportunities to incentivize collaborations with leaders in physics, chemistry, mathematics, and cancer research so that theoretical physics can be used in the battle against cancer. The NCI and the American Association for Cancer Research (AACR) are cosponsoring a cancer prevention think tank event, which will bring together basic, translational, and behavioral research scientists and clinicians to develop a comprehensive cancer prevention strategy that includes technology, emphasizes translational science, and enhances behavioral science. An annual meeting on translational research is being planned for the fall of 2008 and is co-chaired by Drs. Sheila A. Prindiville, Director, Coordinating Center for Clinical Trials (CCCT), and Lynn Matrisian, Vanderbilt University; it will replace the summer SPORE meeting. The Small Business Innovation Research (SBIR) Bridge Award in Drug Development is a new effort to cover the gap between Phase I and II SBIRs and private investment. The mechanism requires matching or greater funds from venture capital; a similar mechanism supported by the National Science Foundation (NSF) has reported great success.

Dr. Niederhuber said that Dr. Matrisian is helping the NCI to integrate the Translational Research Working Group (TRWG) recommendations into the CCCT. A Translational Research Operation Committee (TROC) will be established under the Clinical Trials Advisory Committee (CTAC). TRWG goals are to tailor new and existing programs to facilitate early translation research progress, as well as to improve coordination and collaboration and instill a culture of active, goal-oriented management. Additional objectives are to improve the identification of the most promising early translation research opportunities and enhance the operational efficiency and effectiveness.

NCI initiatives at the Clinical Research Center include continuing to strengthen the medical oncology division and exploring the establishment of a satellite center at Suburban Hospital. Additional activities are the recruitment of a new chief of laboratory pathology, pathology space renovations, development of an Oncology Imaging Center, strengthening of fellowship training, and participation in a rare diseases clinic. The Clinical Research Center had a very successful startup of the first trial in which the PI was an extramural investigator; it is a Phase I/II trial focused on hereditary medullar thyroid carcinoma. With pediatric and adolescent patients from throughout the United States and some foreign locales who are enrolled in the study admitted to the Center, the Clinical Research Center is now truly heralded as a national resource.

Questions and Answers

Dr. Runowicz asked about the rationale for the satellite center at Suburban Hospital, and Dr. Jean deKernion, Professor and Chairman, Department of Urology, and Senior Associate Dean for Clinical Operations, David Geffen School of Medicine at UCLA, queried about the benefits of this collaboration. Dr. Niederhuber responded that this effort is modeled partly after the National Heart, Lung, and Blood Institute's (NHLBI) successful linkage with Suburban Hospital. It allows a more diverse training program for fellows and assists with the recruitment of talented clinician scientists. It also is a means to provide service to patients at the onset of disease; for example, the NCI currently does not focus on protocols that address primary colon or breast cancer patients. Dr. Niederhuber explained that the hospital's marketing strategy benefits from this arrangement and that the NCI does not expect to incur additional costs from it.

Ms. Giusti asked whether the nonprofit community would be permissible as a substitute source for the venture capital funds that SBIR Bridge Award grantees must obtain. Dr. Niederhuber replied that the requirement for venture capital was considered because the intent is to move toward the production

and marketing of products and technologies; another mechanism might be available for partnerships with foundations and the nonprofit community.

In response to Ms. Giusti's question about what one message that he would advocate to be shared during media interviews, Dr. Niederhuber answered that it would be the story of the importance of cancer and its impact on the economy. In addition, he reminded members that the investment made in cancer is an investment in all diseases; the cancer community has been successful in translating its knowledge of cancer diseases, including how the biology of cancer impacts so many other diseases.

Dr. Bruce Chabner, Clinical Director Massachusetts General Hospital Cancer Center and Chief of Hematology/Oncology, Massachusetts General Hospital, supported the integration of the SPORE program under the oversight of the Division of Cancer Treatment and Diagnosis (DCTD) as a means to make better use of resources and as an important area for potential cross-institutional collaboration; emphasis should be placed on the quality of the biology research and the translation to clinical application. Dr. Niederhuber agreed and said that now is the time to bring new thinking and new energy into the program. Dr. Kenneth Cowan, Director, UNMC Eppley Cancer Center, University of Nebraska Medical Center, also favored this change, voiced support for Dr. Matrisian's role in the NCI, and added that during its February meeting, the CTAC discussed better integration between early phase clinical trials and the laboratory, as well as integration between early phase clinical trials and advanced clinical trials. He encouraged the NCI to identify specific translational research ideas to advance rather than work on new, large projects that are less focused.

Dr. Niederhuber expressed appreciation for NCI staff and Division leaders for their collaborative work and support of the Director.

IV. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), reported on the FY 2008 and FY 2009 appropriations status and reviewed legislation of interest to the NCI.

Appropriations Status. The FY 2008 appropriations process was completed on December 26, 2007, allocating to the NIH a budget of $29.3 B and the NCI a budget of $4.8 B. The PB for FY 2009 was announced on February 4, 2008, and it shows no increase for the NIH or NCI. The budget committees and the Ways and Means Committee will examine the overall department budgets in February and subsequently the Appropriations Committees will consider the budgets of individual agencies. The NIH overview hearing is tentatively scheduled for February 26, 2008. Dr. Zerhouni will attend. A realistic timeline for the appropriations process would begin with House bills passed in June or July, Senate bills passed in July through September, and operation under a continued resolution through the November national elections.

Legislation of Interest—1st Session. During the first session of the 110th Congress, the following bills were passed: the Omnibus Appropriations bill (PL 110-161); the Breast Cancer Stamp Reauthorization Act (PL 110-150); the FDA Amendments Act (PL 110-85); and the National Breast and Cervical Cancer Early Detection Program Reauthorization (PL 110-18). The Stem Cell Research Enhancement Act was passed by Congress, but was vetoed. Additionally, some bills are still pending, including the Conquer Childhood Cancer Act, the Breast Cancer and Environmental Research Act, and the Genetic Information Non-Discrimination Act.

The Pediatric, Adolescent, and Young Adult Cancer Survivorship Research and Quality of Life Act (HR 4450) was introduced in the House of Representatives on December 11, 2007, sponsored by Representatives Hilda Solis (D-CA) and Mary Bono (R-CA). This bill includes provisions involving the Department of Health and Human Services (DHHS), NIH, NCI, Centers for Disease Control and Prevention (CDC), and Health Resources and Services Administration (HRSA). The key provisions involve the coordination of NIH activities in survivorship research, with priority given to the following research areas: assessment of the prevalence and etiology of late effects of cancer and treatment; identification of predictors of neurocognitive and psychosocial outcomes, QOL in cancer survivors and families; investigation of the causes of health disparities in childhood cancer research; and evaluation of systems of follow-up care. The bill would allow for the DHHS to give grants to recognized childhood cancer advocacy programs to improve psychosocial care. The CDC, in conjunction with the NCI, will provide guidance to states on interventions that may be incorporated into State Cancer Control programs to improve long-term health status and existing surveillance systems, and HRSA could offer grants to establish pilot programs on model systems for childhood cancer survivor care.

Outlook—2nd Session. Due to the Presidential election, legislative actions for the 2nd Congressional Session are difficult to predict. It is expected that there will be few legislative days and little motivation to compromise to ensure that bills are passed.

Questions and Answers

Dr. Niederhuber noted that this will be the first time that the NCI may not be able to appear at the NIH appropriations hearing. He assured NCAB members that he still will visit with members of the House and Senate appropriations committees. Ms. Erickson commented that there is an effort to have multiple DHHS agency heads at the same table to illustrate their collaborative and collegial relationships. Dr. deKernion asked about the decisionmaking process in regards to attendance at this hearing, and Ms. Erickson responded that it is the Appropriations Committee's decision.

Dr. Runowicz asked whether the pending bill HR4450, which would charge the NCI with overall survivorship research, provided any financial support for this task. Ms. Erickson responded that there was none; even though the NCI would have a role in coordinating the survivorship research conducted by other NIH Institutes, it would not be expected to provide the financial support. Dr. Niederhuber added that often there is a disconnect between the authorizers and the appropriators.

V. AMERICAN ASSOCIATION FOR CANCER RESEARCH (AACR): A SECOND CENTURY OF LEADERSHIP IN CANCER SCIENCE AND MEDICINE— DR. WILLIAM HAIT

Dr. William Hait, President, AACR, expressed appreciation for the opportunity to present to the NCAB, and he praised Dr. Folkman for his years of work in cancer research.

The AACR has collaborated with NCI throughout many years due to their shared missions. AACR's strategic goals to carry out that mission include to: foster the highest quality cancer research; maintain its standing as an authoritative source for cancer research findings; help plan for the cancer workforce of the future; fund both senior and junior scientists; serve as an authoritative voice in matters of great public concern; and develop synergistic national and international partnerships with scientists, physicians, and patient organizations. As the leading cancer research organization in the world, the AACR has the responsibility to be a clear voice for the major scientific and policy issues of the day, most importantly the underfunding of cancer and biomedical research through diminishing growth in the budgets of the NCI and NIH. To deal with these funding cuts, the AACR has established some significant

policy goals in cancer, primarily to restore cancer research as a national priority. It has opened a Washington, DC office to help accomplish this goal. Other key goals are to communicate the economic opportunities in cancer research, advocate for increased funding, work with the U.S. Food and Drug Administration (FDA) to accelerate drug approval, and emphasize the economic and human cost of cancer.

The AACR is celebrating its centennial, and its membership is growing rapidly, with more than 27,000 members in 70 countries. The organization remains committed to women, minorities, trainees, and patients, and also is determined to help reverse the cancer burden in less-developed countries. It has been increasingly focused on translational and prevention research and serves as a think tank on four major issues: culture, human resources, infrastructure, and regulatory processes. The AACR is a dynamic organization and is determined to succeed in accomplishing its goals.

Questions and Answers

Ms. Giusti asked about AACR's funding in general and in relation to meetings and grants. Dr. Hait responded that the AACR has invested approximately $3 M in grants. There is a balance between spending on meetings and this new investment in research.

Dr. Niederhuber expressed appreciation to Dr. Hait for his presentation and for his work during the past year, noting that Dr. Hait has been a great partner for the NCI. The AACR is an important organization that has provided a tremendous base for education and discussion of science. A benefit of the organization's growth is that the resources generated now are being put back into the laboratories. Dr. Hait noted that Dr. Daniel Von Hoff, another AACR past president, serves as an NCAB member.

VI. SPECIAL RECOGNITION OF RETIRING NCAB MEMBERS—DRS. JOHN NIEDERHUBER AND CAROLYN D. RUNOWICZ

On behalf of the NCI, Dr. Niederhuber recognized the service of five NCAB members whose terms of office ended as of this meeting. The retiring members are: Dr. Cowan; Dr. deKernion; Dr. Moon Chen, Associate Director, Population Research and Cancer Disparities, University of California Davis Cancer Center; Dr. Franklyn Prendergast, Edmond and Marion Guggenheim Professor of Biochemistry and Molecular Biology and Director, Mayo Clinic Comprehensive Cancer Center, Mayo Foundation; and Ms. Lydia Ryan, Service Line Clinical Director, Hematology and Oncology/Stem Cell Transplantation, Children's Healthcare of Atlanta.

VII. NIH DIRECTOR'S REPORT—DR. ELIAS ZERHOUNI

Dr. Niederhuber introduced Dr. Zerhouni to the Board. He said that Dr. Zerhouni faced numerous challenges when he became the NIH Director, including the re-education of Congress about the need for the NIH to continue to grow and lead in biomedical research. He thanked Dr. Zerhouni for his support for many years as both a professional colleague and friend.

Dr. Zerhouni began by noting the importance of the NCI and its directorship in terms of the NIH constellation. The advances that have been made in cancer research have had an impact on the understanding of many diseases beyond cancer. He expressed appreciation for the opportunity to provide a sense of the context in which the NIH is operating, describe the events that are driving the NIH and NCI, and share his own priorities for the NIH.

For FY 2009, the NIH is proposed to have a flat budget of $29.5 B, equal to FY 2008. This does not reflect a lack of support for the NIH but rather the lack of money for the country. The budget is a national issue, driven by: 1) entitlement programs, which continue to grow at a pace greater than inflation and greater than the gross domestic product (GDP); and 2) the war economy. Dr. Zerhouni encouraged policymakers and advisory boards to gain a comprehensive understanding of the coming demographic problems to make better decisions. Other concerns include reimbursements on Medicare and Medicaid that will affect physicians and cancer treatment such as the recent issue about radioactive antibodies. Because there appears to be a clear sense that physical sciences have been short changed over time, Dr. Zerhouni said that a unitary concept of science that all advances are really dependent on every field of science should be adopted. The research community should promote all sciences.

Dr. Zerhouni described the priorities that have been established for the NIH's budget. One decision has been to re-allocate $111 M from the National Children's Study for other purposes, such as helping Institutes remain slightly ahead of last year's funding levels, and especially to sustain investigator-initiated research and the number of RPGs as much as possible. He recognized that there are many strong supporters of the Study, including himself, but said that this is a priority decision. Dr. Zerhouni said that he is committed to three additional priorities: 1) new investigators, who as a group tend to be penalized during times of budgetary constraints; 2) the Bridge Award Program to support vulnerable scientists (i.e., young investigators who are up for renewal of their first grant but are 5 percentile points from the payline, or established investigators who have limited resources to sustain their laboratories); and 3) innovation, as the greatest risk in science is to stop taking risks. In 2007, the NIH funded 30 major awards for people who are within 10 years of their doctoral degree, and NIH Institutes are considering ways to continue this support. Dr. Zerhouni said that it also is important for the NIH to allocate 1 to 1.5 percent of its budget to those areas that affect all areas of scientific research. An epigenomics initiative, for example, was started in 2007.

Another priority is the campaign to re-educate Congress about the need to sustain biomedical research and life sciences. The NIH would like to avoid the experience of NASA, which saw funding drop for 15 years after the landing on the moon, and so would like Congress and the public to understand that the NIH is an investment with great returns; the NIH is taking the lead on crystallizing what happens across all fields of science. The NIH's productive work is seen in cancer statistics and the progress made against heart disease. As part of the national priority-setting process, and due to the amount of competition for federal funds and priority setting for federal funds, the NIH has to express a more proactive agenda that clearly articulates the direct benefits and impact of the investment.

Just as the physical sciences presented the greatest challenge for the 20th century, life sciences have implications for plant sciences, environmental sciences, and energy resources in the 21st century. The impact of scientific discoveries is much larger than just health impact and requires a scientific workforce that is competitive worldwide. The vitality of any scientific enterprise depends on well-trained people, and Dr. Zerhouni emphasized the importance of maintaining the synergy between the NIH and the private sector, including the pharmaceutical and biotechnical industries, in the pursuit of discovery.

Dr. Zerhouni shared data concerning demographics of NIH-funded scientists that have policy implications for new investigators. Data from 1980 through 2006 that compared the age of NIH PIs and medical school faculty showed an increasing gap between becoming a faculty member and receiving an NIH grant, and on average, first-time investigators are approximately 40 years in age. This is partly explained by the baby-boom generation, due to which more young workers were entering the workforce in 1980. This raises the question of what will occur when those workers begin leaving the workforce in 2011. Dr. Zerhouni asked actuarials to provide projections about the age distribution of PIs for 2007 through 2020 using standard actuarial models. The models expect more people over the age of 68 to be

funded than people below the age of 38, representing a very different demographic. Consequently, the NIH has prioritized the number of RPGs awarded to encourage the emergence of innovative concepts, maintain national competitiveness, and sustain science.

Dr. Zerhouni also showed data that illustrated that the number of R01 investigators overall is not closely tied to the growth of the budget, but that a strong correlation exists between the number of new R01 investigators and increases and reductions in the budget. In essence, there is a balance in the system that taxes the new investigator and invests in scientists with a proven track record. Because of a significant decrease in the number of new investigators since 2004, the NIH and Institute and Center (IC) Directors have decided to maintain a floor of about 1,523 new investigators per year across all of the NIH. Because the number of applications has doubled, there will be pressure to maintain the application success rate. The goals in 2007 were to stabilize the number of competing grants and strengthen the support for at-risk investigators. Dr. Zerhouni asked the NCAB to remain cognizant of the historical trends and understand NIH's strategic rationale for its decisions about the prioritization of funds.

Questions and Answers

Dr. Chabner asked about the shift in terms of dollars to the expected increase of older investigators being funded. Dr. Zerhouni responded that this phenomenon is partly from the behavior of the system, different growth rates, and resource distribution. The NIH has discussed this issue, and both the Advisory Committee to the Director led by Dr. Yamamoto and a separate group of Institute representatives, are preparing recommendations on the issue.

Dr. Cowan observed the large number of foreign-trained individuals who have immigrated to the United States and asked Dr. Zerhouni to share his thoughts on programs to encourage young students to consider science as a career. Dr. Zerhouni said that the most valuable resource to the NIH is talented people, and the NIH invests heavily in them. It is important for the NIH to promote K-12 science education, given the 17 million job positions, such as nurses, health providers, and scientists, that are expected to be unfilled by 2020 and the large percentage of the workforce that will be eligible for retirement within the next several years.

Dr. Niederhuber asked Dr. Zerhouni to comment on the discussion during Speaker Rep. Pelosi's recent health forum about the correlation between fewer real dollars in the NIH budget and the reduced number of funded scientists. Dr. Zerhouni said that scientific issues require human creativity; even with great advances in technology, the costs associated with personnel will not be reduced. He requested that the NCAB and other advisory boards consider issues surrounding new investigators and innovative science with sensitivity during discussions and recommendations about specific programs.

Dr. Anna Barker, Deputy Director for Advanced Technologies and Strategic Partnerships, asked about Dr. Zerhouni's thoughts on the impact of the globalization of science. Dr. Zerhouni said that the United States currently is the most desirable destination for creative scientists, and he noted that approximately 9 of 10 scientific staff in foreign research agencies have received some training in the United States. Many countries, however, are reforming their scientific communities; Australian universities, for example, have nearly doubled the total number of their students from 500,000 in 1996 to 900,000 in 2007. Globalization means a knowledge economy, and the capacity around the world has been rebuilt. The investment in infrastructure is key to this.

Dr. Chabner wondered about an overall NIH plan to develop a long-term solution to sustain the Clinical Research Center as an attractive and viable research entity. Dr. Zerhouni commended Dr. Niederhuber and the NCI for providing leadership in this area and for raising the topic with the NIH

Steering Committee. A subgroup of the Steering Committee under the direction of Dr. Steve Katz is examining the three possible courses of action: increase revenues, decrease expenses, and change the operating model. Increasing revenues is difficult to achieve in a nonprivate enterprise. Expenses have been reduced, and the Center's budget has been flat for the past 3 years. Dr. Niederhuber said that the Center is an extremely valuable laboratory for the NIH, serves as a beacon for scientists who might want to work at the NIH, and is expected to be a critical part of the translational research program. It is important to give careful consideration to any decisions that will impact the Center. Dr. Zerhouni agreed and emphasized that there is an increasing need to tie intramural clinical center activities to extramural activities.

Ms. Giusti recalled a prior comment from Dr. Niederhuber that the current budget issues faced by both the NIH and NCI likely will continue for the intermediate term; she asked whether Dr. Zerhouni anticipated additional risks for the NIH or NCI. Dr. Zerhouni replied that the current situation is one of a structural phase of difficulty, rather than a tactical phase that is caused by a single factor or individual. The main driver for improved conditions is the growth of the economy; he strongly urged Institute Directors and advisory boards to consider cancer research through a forecast perspective of 5 years or longer. He stated that the NIH budget is an investment, not a subsidy.

Drs. Niederhuber and Runowicz expressed their appreciation to Dr. Zerhouni for meeting with the NCAB.

VIII. ANNUAL DELEGATIONS OF AUTHORITY—DR. PAULETTE S. GRAY

Dr. Gray asked for concurrence by the NCAB on two Delegations of Authority to the Director of the NCI. She described the delegations and the provisions in the Statement of Understanding. Delegation A allows the Director to obtain the services of not more than 151 special experts or consultants who have scientific or professional qualifications. Delegation B specifies that the NCI Director can appoint advisory committees composed of private citizens and officials of Federal, State, and local governments, including membership of task forces, working groups, and other bodies.

The Statement of Understanding with NCI Staff on Operating Principles in Extramural Grants also falls within the Delegations of Authority to the Director, NCI. The NCAB operations are conducted in accordance with management and review procedures described in the NIH Manual Issuance 4513. Concurrence of the NCAB with recommendations of initial review groups will be required except for the following: 1) Training grants and fellowships and other non-research grant applications are not subject to NCAB review and approval and without other concerns may be awarded without presentation to the NCAB for concurrence with the exception of Ruth L. Kirschstein National Research Service Awards. 2) Applications over the 50th percentile will not have summary statements presented to the NCAB. 3) For applications assigned raw scores that are not percentiled, the cutoff will be a priority score of 250 for all mechanisms except R41, 42, 43, and 44 awards; for the latter, all scored applications will be included. Expedited Concurrence: 1) for R01 and R21 applications with percentiled or raw scores that fall within the NCI paylines for that mechanism, a process of expedited concurrence will be used; and 2) the Executive Secretary will alert Board members with responsibility for expedited concurrence when review outcomes for eligible applications are available on the Electronic Expedited Concurrence portion of the Electronic Council Book. Administrative Adjustments: 1) Permission is delegated to the Director, NCI, to allow staff to negotiate appropriate adjustments in dollars or other terms and conditions of grant and cooperative agreement awards. 2) Administrative requests for increases in direct costs that are the result of marked expansion or significant change in scientific content of a program after formal peer review will be referred to the Board for advice and recommendation. 3) Actions not requiring Board review or advice, such as change of institution, change of principal investigator, phase-out or interim support, or additional

support need not be reported to the Board. 4) NCI staff may restore requested time and support that were deleted by the initial review group when justified by the principle investigator in an appeal letter or restoration is in the best interest of the NCI and the project is of high NCI programmatic relevance.

Motion. A motion was made that the NCAB concur in granting authority to the Director, NCI, as specified in Delegation A and Delegation B and to concur in the Statement of Understanding with NCI Staff on Operating Principles in Extramural Awards. The motion was seconded and approved unanimously.

IX. UPDATE: THE CANCER GENOME ATLAS—DRS. ANNA BARKER, DANIELA GERHARD, LYNDA CHIN, CAMERON W. BRENNAN, JOE W. GRAY, AND RICHARD K. WILSON

Dr. Barker reminded the Board that The Cancer Genome Atlas (TCGA) is co-sponsored by the NCI and the National Human Genome Research Institute (NHGRI) and functions as a network with seven Institute members funded by the NCI and three by the NHGRI. The activity actively integrates scientists and physicians who work in molecular biology and genetics, sequencing, biostatistics, and bioinformatics. The network has agreed on standard extraction processes to ensure that all biomolecular specimens have equal quality. In addition, a data coordinating center provides a centralized data management system for the project.

Dr. Daniela Gerhard, Director, Office of Cancer Genomics, NCI, introduced the speakers: Drs. Lynda Chin, Associate Professor, Dana-Farber Cancer Institute, Harvard Medical School; Cameron W. Brennan, Analysis Co-Leader, Neurosurgical Service, Memorial Sloan-Kettering Cancer Center; Joe W. Gray, Associate Laboratory Director, Life and Environmental Sciences, and Director, Life Sciences Division, Lawrence Berkeley National Laboratory; and Richard K. Wilson, Professor of Genetics and Director, Genome Sequencing Center, Washington University School of Medicine.

Glioblastoma: The Disease. Dr. Chin explained that TCGA is working to define the atlas of genomic and epigenetic changes in glioblastoma multiforme (GBM), lung, and ovarian cancers to identify subtypes that can stratify patients for therapy, discover predictive or prognostic biomarkers, identify rational targets for therapeutic intervention, and improve the survival of patients. She provided basic information about GBM, which is one of three cancers currently targeted by TCGA. Primary brain tumors are not a high-incidence disease, accounting for only 2 percent of all primary tumors; however, this tumor ranks fourth on the impact of disease with respect to life years lost. The most common of these tumors are the gliomas, which include astrocytoma, oligodendrogliomas, or a combination of these. There are 17,000 new cases and 12,000 deaths each year in the United States. The World Health Organization (WHO) defines GBM as grade IV, with a median survival of 9 to 12 months and a 2-year survival rate of 4 to 15 percent. Dr. Chin observed that only limited progress against this cancer has been made during the past 15 years. There are two clinical subtypes of GBM: 1) primary GBM, which accounts for 90 percent of diagnosed patients; and 2) secondary GBM, which begins as a lower grade glioma and progresses. Secondary GBM can be stratified into two distinct subclasses with a different time to progression. A goal of TCGA is to define the subclass of primary GBM on the genomic level.

Dr. Chin described the state of clinical management for GBM patients through an example of EGFR, which is amplified in approximately 43 percent of GBM. About one-third of those amplified tumors have a unique signature mutation called the EGFR-vIII, which is a constitutively active receptor where exon 2-7 of the extracellular domain has been deleted deleted. Recent high-throughput sequencing has identified a new extracellular domain mutation in about 14 percent of the tumors studied. This implies that GBM should be a disease that can be targeted with the tyrosine kinase inhibitor (TKI) against EGFR,

but a Dana-Farber study found that, after 2 months of treatment with Iressa(r), tumors grew larger. One explanation is that there are many other alterations in the genome in addition to EGFR, and the PTEN tumor suppressor may be targeted. Subsequent studies showed that PTEN status is a molecular determinate of therapeutic response to EGFR inhibitor; 83 percent of responders in a study were shown to have intact PTEN expression in contrast to those who did not respond, thus highlighting the value of defining the subset of patients who have intact PTEN and will respond to EGFR inhibition. Another explanation for the meager response to TKI in GBM is that other receptor tyrosine kinases (RTK) are activated simultaneously in GBM and maintain the signaling, and so EGFR inhibition has no effect on AKT signaling. This suggests a new therapeutic strategy to target multiple RTKs to effectively extinguish signaling through PI3K. In addition, the co-activation of RTK on the protein level is supported by genomic data. GBM involves a complex and deregulated signaling pathway that appears to be driven by underlying genetic and epigenetic alterations; GBM researchers believe that cancer ultimately is a disease of genes, and there are many alterations present in the cancer genome.

Genomic Aberrations in GBM From TCGA Pilot Program. Dr. Brennan said that copy number aberrations (CNA) often are observed in malignant tumors. Data collected by four centers that are analyzing copy number and loss of heterozygosity are of high quality and reproducible across both centers and platforms. This concordance indicates that the quality of DNA analyzed in this work is exceptionally high, and implies excellence in tissue collection and banking. Primary and secondary GBM tumors were analyzed to identify changes in copy number and to determine if these tumors could be classified into clinically distinct categories. Copy number analysis found three stable clusters: gain of chromosomes 19 and 20, loss of chromosomes 13 and 14, and gain of chromosomes 7 and 10.

These copy number profiles were ranked by the five different classes determined by analysis of tumor transcriptome data. The profiles characterized by gain of chromosomes 19 and 20 and loss of 13 and 14 were enriched in two different transcription classes and thus may represent two different types of tumors. Alternatively, the gain in gene dosage from chromosomes 19 and 20 could impact the transcriptome; this can be determined by controlling for gene dosage and re-clustering the profiles. Although significant differences in survival among GBM patients has not been evident clinically, plotting the association of gain or loss in the genome with better or poorer survival showed that for certain regions of the genome, gain was associated with poorer survival and loss with better survival. Although complete profiles were not associated with survival, small regions of the genome may correlate with survival.

These data can be used to identify focal events that could suggest new sequencing targets. A summary of 165 tumors found peaks indicative of specific deletions, such as deletion of p16. Analysis of this data using a gene set enriched for oncogenes found changes at the loci of common oncogenes such as EGFR, PDGFR, KIT, MET, and two forms of AKT, among others. A similar analysis can be performed for tumor suppressor genes; this approach identified alterations at the loci for PTEN, all three CDKN2 family members, RB, and others. This technique also is powerful enough to identify specific focal events within a gene. For example, deletions within the EGFR gene can be mapped to specific introns. A terminal deletion in the PDGF receptor was mapped to an area covering less than 600 base pairs. Fusion events, which often result in creation of a constitutively active molecule, also can be identified.

Transcriptional Subsets: Integrative Approaches and Opportunities. Dr. Gray stated that GBMs were profiled using three different expression profiling platforms while changes in methylation at approximately 1,500 loci also were investigated. Transcriptional profiles were developed for 160 tumors, and they showed that the tumors fall into three or four clusters. These clusters were not platform dependent, as shown by pair-wise comparisons between the different Centers performing these analyses. Comparison of the four clusters defined by transcriptional profiling with two microRNA clusters showed some association between the microRNAs and gene expression.

The exon array platform used in the LBL experiments permits interrogations of the transcriptome on an exon-by-exon or even within-exon basis. This allows investigators to determine if a given cluster includes alternatively spliced or express subparts of a gene differently than others. Expression patterns for many tumors showed that some transcribe parts of a given gene at a different level than others. A statistic, Finding Isoforms using Robust Multichip Averaging (FIRMA), has been developed that allows conversion of exon expression into a variability indicator. This method can be used to generate a heap map that indicates the position within the gene that is the site of variable expression and facilitates comparison among tumors.

Attempts are underway to integrate these data with other platforms in use through the TCGA project. The EGFR showed that variants in transcription can be observed at the same site at which changes in copy number were determined. This indicates that the chromosomal deletions are transmitted to the transcript, and is therefore likely to have a biological function. Transfection of NIH3T3 cells with a particular EGFR deletion identified by this approach resulted in increased colony formation by these cells, indicating that the deletioned versions of EGFR are biochemically active in the absence of EGF and thus have rendered the cells EGF-independent.

Data from transcriptome profiling also can be integrated with data from sequencing centers. Analysis of the OAS1 gene found two different readouts associated with a particular exon, which were attributed to a single nucleotide polymorphism (SNP) within the gene, rather than transcriptional differences. In another case, a mutation in p53 found by sequencing did not show an effect at the transcriptional level. It was determined that this mutation introduced a premature termination codon, and likely leads to nonsense-mediated degradation of the gene, resulting in loss of that transcript. Analyses such as this can help distinguish between gain-of-function mutations, or dominant-negatives, and those that inactivate genes. This approach will help validate mutational data from sequencing centers and also provides biological information about the behavior of these mutations.

Work also is underway to integrate the degree of methylation and expression. Such an analysis can determine whether a change in expression is associated with changes in methylation at a given locus. This work will help to provide an understanding of how epigenomic changes affect the transcriptome.

Sequencing the Cancer Genome. Dr. Wilson said that the polymerase chain reaction (PCR)-based re-sequencing process involves the generation of a list of candidate genes and the gathering of a collection of genomes from patient samples to examine for changes in the tumor DNA that might be associated with the disease. The first phase of the targeted re-sequencing in GBM included literature search and the use of unpublished data that resulted in the identification of approximately 600 genes to re-sequence. The second phase involved initial GBM genome characterization data by CGCCs, genetic elements of interest defined by analysis of copy number and expression in GBM across multiple platforms, conserved regions across evolution, and tumor-specific spliced variants; the Phase II list contains an additional 702 genes added to the pipeline for re-sequencing. To compare data quality between centers, three centers sequenced the same set of 20 genes with 84 tumors. The intention was to validate any mutations found in this process through other genome-based technologies. TP53, PTEN, and EGFR had high frequencies of mutations as well as putative somatic mutations in a number of other genes.

Next generation DNA sequencing technologies include the 454 FLX and Solexa sequencers. These machines are a significant improvement over the older applied biosystems 3730 sequencer. The 454 FLX yields 400,000 sequence reads per run, and needs 360 runs to process 100 million bases per run; the cost per run is approximately $6,800, for a total cost of almost $2.5 M. The Solexa provides 40

million sequence reads per run, and needs 59 runs to process 1.28 billion bases per run; the cost per run is approximately $9,300, for a total cost of nearly $550,000. The 454 FLX requires about one-half of the amount of data for genome processing that the Solexa needs. The 454 FLX technology has been used to validate K-ras and EGFR mutations found during PCR-based GBM sequencing. Another application is the ongoing collaboration between Baylor Center and Nimblegen on exon sequencing, which involves building a chip or array that has representative bits of sequence down to the solid phase and sequencing just the exons, rather than the entire genome. The Solexa instrument can be used for whole genome sequencing. To discover, for instance, the difference between the tumor genome and the normal or wild-type genome from the same patient, the DNA is sequenced in bulk and then compared to determine differences.

These technologies have been used outside TCGA to sequence the genome of an acute myelogenous leukemia (AML) patient who relapsed and died after 11 months. A careful survey of the patient's family showed a family history of colon cancer (mother), lymphoma (uncle), alveolar cell cancer (uncle), and AML (uncle). The AML tumor genome sequence obtained 77 percent diploid coverage with 22x sequence coverage; there is a 10x sequence coverage of normal genome. Approximately 2.1 million sequence variants were detected, with nearly 495,000 being novel. Of these variants, 3,700 are non-synonymous, meaning that they change amino acids in coding sequences; most of these likely are rare SNPs. Two somatic mutations—FLT3 and NPM1—have been found and confirmed, and both are small insertions within coding sequences. Both have been implicated previously in myeloproliferative disease. Currently, the research is validating a small number of additional candidate somatic mutations. Dr. Wilson explained that these instruments have been used to look at cDNA sequences or transcriptomics from the same patient. The same mutations have been noticed in both the cDNA and genomic DNA. This also can be used as a method to detect alternative splicing.

Translation of TCGA Data. Dr. Chin summarized the progress of the project thus far. The atlas of changes in human GBM has begun to be defined through deeper insights into known mutations, identification of novel gene candidates, and cross-platform validation of alterations. Additionally, distinct molecular subtypes of primary GBM have been defined, and new technology for sequencing provides more and better data at a lower cost. TCGA itself and the data generated within the center will inform GBM, and it will take from and inform all the other activities in the cancer community, including model organisms, human systems, and clinical associations. The integration across GBM, lung, and ovarian tumor types also will inform each other. Dr. Chin concluded with an example of kinases in a GBM tumor cell line through RNAi screen, cancer genome data, and developmental insight to illustrate how the multidimensional genomic data in TCGA is envisioned to integrate with various developmental biology and cancer biology from the community.

Questions and Answers

Dr. Runowicz asked about methods of collaboration. Dr. Barker replied that a project team from the NCI supports TCGA and the GBM effort. Dr. Chabner asked about interactions between the working group addressing GBM biology and TCGA GBM activity, as well as about the structured relationship with the National Brain Tumor Clinical Trials (NBTCT) group. Dr. Chin confirmed the importance of linking TCGA's GBM work with GBM biological efforts, and she explained that several experts serve both on TCGA and NBTCT. Dr. Barker added that SPOREs investigators also are helping TCGA with GBM tissue and pathology issues. Dr. Chabner voiced support for these various collaborations, noting that they will help resolve biologic questions that scientific review committees ask during the review of clinical trial protocols of new drugs for GBMs.

Dr. Daniel Von Hoff, Physician in Chief and Senior Investigator, Translational Genomics Research Institute and Clinical Professor of Medicine, University of Arizona, Arizona Cancer Center, encouraged TCGA to provide resulting findings to physicians whose patients donated GBM and are survivors. Dr. Barker said that informed consent forms are sensitive to this issue and that TCGA has plans to examine a group of fairly long-term GBM survivors. Dr. Von Hoff also asked about the rationale for a monetary donation to Washington University from a businessman that Dr. Wilson described during the presentation. Dr. Wilson replied that the donation was unrelated to the patient who benefited from the work in PCR-based sequencing that it supported.

Dr. Cowan asked whether there will be correlations of the data made with biomarker discovery. Dr. Barker indicated this was likely, given the current attention to biomarkers, and she recognized the need to organize biomarker discovery holistically, based on an understanding of the genomic changes that are relevant through the transcriptome and proteome. Dr. Joe Gray said that it is expected that information about cancer-specific abnormalities will flow into biomarker efforts as rapidly as the information is available. Dr. Donald Coffey, The Catherine Iola and J. Smith Michael Distinguished Professor of Urology/Oncology/Pathology/Pharmacology and Molecular Science, John Hopkins University School of Medicine, said that the vast complexity of these tremendous methylation pattern dynamics, rather than sequencing, will pose the greatest challenges in the genome arena. Dr. Barker stated that the bioinformatics grid has been a tremendous boon to handling the emerging data. Dr. Gerhard added that the NCI has issued an RFA regarding the development of new analytical tools in recognition of large-scale data generation.

Dr. Chabner said that a way to simplify the process of acquiring survival and proliferation signals is to identify the receptor kinases that are activated in a given tumor and then study the genome to determine whether the issue is related, for example, to methylation or epigenetics. Dr. Brennan said that mutations seen in two tyrosine kinases can be expanded beyond tyrosine kinases, and thus genomics partly informs about the pathways that are being requested for additional mutations by the tumor as it evolves; genomic data also are highly useful for the identification of a subgroup of tumors and determination of active signaling. Dr. Chin added that the coactivation of RTK was observed in a majority of solid tumors that Dr. dePinho has examined; studies continue to ascertain the percentage of coactivated RTK that are driven on the genetic versus translational levels.

X. CENTER FOR CANCER RESEARCH (CCR) GENOMICS INITIATIVES—DR. PAUL MELTZER

Dr. Paul Meltzer, Adjunct Investigator, National Human Genome Research Institute and Senior Investigator and Chief, Genetics Branch, CCR, NCI, presented information on new genomic initiatives. Genome scanning has been ongoing for many years using the traditional G-banded karyotype scan. It has been recognized for decades that the cancer genome is often severely altered. Cancer is essentially a disease of disordered genome function. Hidden within the chaos are drivers of cancer progression that might be targeted therapeutically. The investigation of the cancer genome could yield significant findings that provide practical clinical benefit, such as was the case with the work of Nowell and Hungerford in 1960 that led to the eventual release of Gleevec® in 1996; many clinicians would prefer to accelerate the pace of biologic discovery and translation. Point mutations, methylation abnormalities, chromosome translocations, and copy number changes are some of the changes at the DNA level that can result in highly abnormal genome function. There are two active approaches to cancer genetics: 1) the identification of inherited variants in the genome that increase cancer risk (i.e., genetic association), and 2) the identification of the differences between the tumor genome and the normal genome (i.e., tumor profiling). The interaction between these two approaches remains to be explored. Cancer genomics is tasked with defining genes that are targets of mutation, mechanisms of genomic instability, and

phenotypic consequences, and then translating this knowledge into the clinical arena. Microarray technology has been adopted with tremendous enthusiasm by the community as seen by the number of citations found in PubMed; the field continues to change rapidly, and sequencing technologies may supplant arrays in many applications. Scientific impetus for genomics initiatives in the CCR includes: the development of clinically relevant molecular signatures for disease, diagnosis, and prognosis; the need to develop predictive biomarkers for targeted therapies; proven implications of tumor genomics for the identification of molecular targets; and progress in Genome-Wide Association Studies (GWAS) of cancer risk as well as in TCGA. Other factors are the number of new and maturing technologies and an extremely strong group of investigators within the CCR who are committed to this research.

A recent CCR initiative is the development of the Center of Excellence in Integrative Cancer Biology and Genomics to promote the innovative use of genomics technologies for basic science discoveries and clinical research applications. It will focus on strengthening NCI's intramural research, enhance collaboration, consolidate existing cancer databases, promote the use of animal models, expand core facilities, and provide a venue for national and international interactions. A Steering Committee, chaired by Dr. Snorri Thorgeirsson, has been established to oversee work in biomarkers and molecular targets, genomics approaches, human genomics and genetics, cancer information, and integrative/system biology and bioinformatics.

The Clinical Molecular Profiling Core, another CCR program, provides CCR investigators with access to state-of-the-art molecular profiling technologies, particularly genome technologies, for biospecimens collected for clinical trials. Research goals include tumor classification and class discovery, the discovery and validation of predictive and prognostic markers, cancer gene discovery, pharmacodynamic markers, hypothesis-based exploration of genes and pathways, and clinical correlation of laboratory-based observations. Dr. Meltzer described the Core's functioning structure from protocol to analysis as well as technologies available for assays.

Dr. Meltzer next discussed integrated cancer genomics, which encompasses gene expression, transcription factor activity, DNA methylation, sequence variation, chromatin modification, and gene copy number. To move beyond lists of genes, it is necessary to use gene annotations and public data efficiently, incorporate data from model systems, and link expression data to sequence. Most importantly, other types of genome scale data should be added. Gene copy number has reached a state of high technological perfection in which the entire genome can be mapped at high resolution on a case-by-case basis; the data are stable and reliable. In sequence variation, the impact of incorporating SNP data into copy numbers is not yet known.

Chromatin modification likely will be one of the most useful ways to annotate the genome. Recent investigations have intertwined tiled microarrays with next generation sequencing technology. The patterns of open chromatin, as mapped by DNAse hypersensitive sites in CD4 positive T cells, were examined and many thousands were mapped. The data show that about 39 percent are intergenic and may correspond to regulatory elements that are not otherwise well mapped at this time. In looking for gene ontology categories that do not contain DNAse hypersensitive sites, functions have been found that are not active in
T cells such as visual or olfactory function, indicating that these groups of genes are silent in T cells. Moreover, an oscillating pattern is revealed when data are aggregated from the preparation of DNAse-treated chromatin and the ensuing cleavage at the hypersensitive site; the frequency of the oscillating pattern corresponds precisely to one turn of the double helix, thus exposing the minor groove of the DNA as it wraps around the nucleosome and is accessible to cleavage. Histone mapping also has been performed and likely will be important for the regulation of gene activity.

Questions and Answers

Dr. Robert Wiltrout, Head, Experimental Therapeutics Section, Laboratory of Experimental Immunology, NCI-Frederick, stated that, with the use of the state-of-the-art Clinical Research Center, the intent is to derive as much information as possible from each patient. Dr. Lloyd Everson, Vice Chairman and Member of the Board of Directors, US Oncology, Inc., Houston, TX, wondered how many clinical and basic research institutions and private and nonprofit companies are working to meet clinical research infrastructure needs. Dr. Niederhuber said that the time might be right for the NCI to take a leadership role in setting up two centers in the United States that would serve as neutral resource sites and still be able to remain current with changes in proteomics and genomics, as well as across the paradigm of technology; he noted that this idea was discussed by the CTAC. He added that this provides to the NCI the opportunity to level the playing field for investigators and establish standardization and quality control that might not be achieved otherwise. Dr. Chabner commented that such centers would facilitate both focused and broader approaches to genomic analysis that could be valuable for the NCI's Phase I and II programs. Dr. Barker said that the NCI will approach this activity in an organized and systematic, CLIA-like way to ensure
high-quality results. Ms. Giusti described her foundation's successful two-prong approach of prospective and retrospective clinical data collection. Dr. Cowan expressed support for NCI's leadership role in developing such a center of excellence to which researchers could send best ideas and specimens, as well as participate in a fee service to correlate with the best clinical science to extract the greatest amount of information.

Dr. Von Hoff described a clearinghouse concept that works well; an important factor in its success is that the assays are performed by pathologists in CLIA-certified laboratories. Dr. deKernion asked about the progress made in obtaining the correct samples. Dr. Carolyn Compton, Director, Office of Biorepositories and Biospecimen Research, NCI, replied that the greatest challenge has been investigators proving that they have samples that are high quality.

XI. UPDATE: CLINICAL PROTEOMICS TECHNOLOGY INITIATIVE FOR CANCER—DRS. ANNA BARKER, HENRY RODRIGUEZ, STEVEN A. CARR, AND DANIEL C. LIEBLER

Dr. Barker stated that researchers believe that many of the biomarkers sought in the fight against cancer will be found in the proteome. The science of proteomics is in its infancy and, in addition to biomarkers, reagents and quality biospecimens are needed. The project was initiated to develop a sound basis for the discovery of biomarkers; validation will occur through other means. The Board of Scientific Advisors (BSA) supported the project, noting that the rigor in proteomics needed to be established for the field to move forward. Dr. Barker introduced the presenters: Drs. Henry Rodriguez, Director, Clinical Proteomic Technologies Initiative, Office of Technology and Industrial Relations, NCI OD; Steven A. Carr, Director of Proteomics, Broad Institute of MIT and Harvard University; and Daniel C. Liebler, Director, Ayers Institute for Precancer Detection and Diagnosis, and Professor of Biochemistry, Pharmacology, and Biomedical Informatics, Vanderbilt University Medical Center.

Overview. Dr. Rodriguez said that the project has three distinct components: 1) CPTAC Centers, which are a network of laboratories that serve as clinical proteomic technology centers of excellence throughout the United States and provide expertise in mass spectrometry; 2) the development or enhancement of technologies and the development of algorithm computational sciences that assist individual investigators; and 3) a reagents and resources core. Five leading centers currently comprise the network: the Broad Institute of MIT and Harvard, Memorial Sloan-Kettering Cancer Center, Purdue University, Vanderbilt University School of Medicine, and the University of California at San Francisco.

These institutes in turn interact with many partners, and this level of networking provides a greater richness in the portfolio of the various technologies that the project can examine. Integration with investigator grants includes support in the development of computational tools and platforms. Examples of work in reagents include antigen and monoclonal antibody production, antibody characterization and validation, and hybridoma and antibody distribution.

Challenges of Clinical Proteomics and Path Forward Defined by the CPTACs. Drs. Carr and Liebler provided details about an inter-laboratory project that has been ongoing among the various centers. At the launch of the program in 2006, clinical proteomics faced several questions regarding whether proteomic methods can detect "signal," the type of samples best suited for proteomics-based discovery, and the process to move to clinically useful markers. Pattern-based and identity-based methods using blood have been found to be limiting and hence raised the question of whether blood was the best sample for biomarker discovery. Tissue and biofluids proximal to the tumor also are candidate samples. In considering whether mass spectrometry, rather than blood, could provide the bridge between discovery and the clinic, system and technical barriers were identified and include issues of biospecimen quality, systematic coordination in biomarker discovery and analyses, and insufficient tools. Moreover, discovery leads to candidates, not biomarkers, and candidates still must be confirmed and quantified in blood.

In October 2006, CPTAC teams began to develop plans for the technology assessment of proteomics and design studies to address unbiased discovery and verification. Key questions focused on the representation of proteins, reproducibility of various discovery and verification platforms, the platforms' measurement endpoints, and the impact of matrix complexity. Specifically, reproducibility and sensitivity for proteomics platforms were to be measured by protein detection and coverage as well as protein quantitation; metrics for statistically significant differences include the number, identities, and magnitude of differences observed, ideally determined as a function of the protein's concentration. Working groups have been established to consider the design of experiments, selection and production of matrices, post-translational modifications, data analysis and storage, and biospecimens.

Two of the working groups are addressing unbiased discovery and platform assessment for targeted verification. The approach is to use "shotgun" proteomics, which is similar to examining jigsaw puzzle pieces to create a picture; this is analogous to shotgun genome sequencing. In the proteome, however, there are many different pictures with one picture for each gene coding sequence, and the pictures are present in multiple copy numbers. Tandem mass spectrometry is used to identify peptide sequences. The goals of the Unbiased Discovery Working Group are to establish performance standards, develop standard operating procedures for shotgun analyses, assess platform performance and detection efficiency for model biomarkers, and implement standardized data analysis tools. Since November 2006, six studies have been ongoing to meet these goals through the systematic evaluation of discovery platforms, development of cell models for marker discovery and verification, selection and production of protein standards, and work in targeted protein quantitation. A process exists for candidate verification in plasma by targeted mass spectrometry. The Targeted Verification Working Group aims to establish performance standards, develop standard operating procedures, generate datasets to develop metrics, identify and resolve sources of variation, and assess assay precision. Next steps for inter-laboratory verification studies include the evaluation of methods to increase MRM assay sensitivity, determination of the extent to which assays can be multiplexed, test of immunoaffinity enrichment, development of MRM assays for several breast cancer proteins, and building of a reagent collection of peptides and antibodies.

Additional information is available in the online scientific article "CPTAC Awardees Tackling Reproducibility, Quantification to Resolve Bottlenecks" by Tony Fong (*ProteoMonitor* 2008;8(8): February 21, http://www.proteomonitor.com/issues/8_8/).

Questions and Answers

Dr. Coffey asked whether a strategy existed to find surrogate markers that can help predict the effectiveness of the therapy on the growth of the cancer. He also queried about the kinetic analysis in CPTAC proteomics. Dr. Liebler responded that, assuming surrogate markers are proteins, the technology for analyzing protein markers is important; the intent is to define and standardize the performance of a platform that would be used to find markers. Dr. Barker noted that one of the critical needs is not the discovery of protein biomarkers but rather that thousands of biomarkers are being discovered that are not reproducible; the issue is to build the technology and the science to meet this challenge. Dr. Carr agreed on the importance of discovering markers for the early detection of disease as well as surrogate markers. He noted that single markers for complex disease probably will not be a paradigm in the future and added that kinetic information can be achieved in a temporal fashion within the same patient over time if a panel of proteins related to a disease can be measured robustly at levels at which they are required to be detected. Dr. Barker said that she has been collaborating with a group of breast cancer clinicians and cell biologists and the FDA on how to design a trial around biomarkers, and that all parties have realized the need for more robust technology and data.

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 recommendation was affirmed by all serving Board members present. During the closed session of the meeting, a total of 1,720 applications were reviewed requesting support of $528,494,781.

WEDNESDAY, FEBRUARY 6, 2008

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

Dr. LaSalle Leffall, Jr., Chair, President's Cancer Panel (PCP, the Panel) and Charles R. Drew Professor of Surgery, Howard University Hospital, announced that the Panel's 2006-2007 annual report entitled *Promoting Healthy Lifestyles: Policy, Program, and Personal Recommendations for Reducing Cancer Risk* is available to Board members. In addition to finalizing the 2007-2008 report, the Panel held four meetings during 2007-2008 that addressed Strategies for Maximizing the Nation's Investment in Cancer. Dr. Leffall thanked Dr. Niederhuber, Dr. Chen, Ms. Giusti, and Dr. Everson for their participation and contributions to the Panel during this series. The most recent meeting was held on January 28, 2008, in New Orleans; this was Mr. Lance Armstrong's last meeting as a Panel member. However, no information is available yet on who will replace him. He will continue to serve until a replacement is appointed.

The common themes that the Panel covered during the past year were: the role of the NCI in the Nation's cancer enterprise; patient-centered cancer research and care; coordination across the cancer

enterprise; innovative scientific discovery; and application of current knowledge. Other common themes included access to quality cancer care for all; smoking cessation and prevention; regulatory barriers; technology development and application; workforce issues; sharing knowledge and resources; strong leadership; and the need for a unified message and vision. The Panel is in the process of preparing its final conclusions and recommendations from this series of meetings; a final report will be presented to the President this summer. The Panel hopes to have this completed by June to present to the American Society of Clinical Oncology (ASCO) meeting.

The 2008-2009 meeting series will focus on Environmental Factors in Cancer. Meetings will be held only in cities with smoke-free environments. Dr. Leffall explained that this sends a strong message, and it encourages communities to pass legislation creating smoke-free environments. The focus of the meetings will be cancer-causing pollutants found in air, soil, food, and water; workplace exposure to arsenic, asbestos, and cadmium as well as job-specific chemical use; and other factors such as nuclear fallout, electromagnetic fields, and radiation exposure.

Potential outcomes of this series are to: determine the role of the NCI as it relates to environmental causes of cancer; identify research needs and potential new areas of collaboration among federal agencies; increase public awareness of environmental and occupational hazards; and develop recommendations for regulating toxic and other potentially hazardous chemicals and materials, reducing exposure to cancer-causing pollutants. Dr. Leffall directed the Board to the Panel's web site (http://pcp.cancer.gov) for further information.

Questions and Answers

Dr. Niederhuber stated that the NCI is grateful to Dr. Leffall for his efforts in keeping the PCP connected to the NCI, and for agreeing to extend his term on the Panel. He also suggested that the environmental issues be extended to include exposures to infectious agents and their impact on immune systems and consequently immune surveillance. Dr. Niederhuber commented that he works on a committee with Dr. Ralph Steinman, Henry G. Kunkel Professor and Senior Physician, The Rockefeller University, who concurs that more work needs to be conducted on the immunological role relating to cancer. Dr. Leffall said that he would present the suggestion to members of the PCP.

Ms. Giusti agreed with Dr. Niederhuber, and she advocated for more action-oriented discussions. She attended the PCP meeting in New Orleans and noticed that, although presenters consistently mentioned the role of the patient, patients often do not understand their role. The community could improve its efforts in helping patients understand why they should donate tissue or participate in a trial. She noted that Mr. Armstrong is a very powerful voice and a person whom patients trust. The PCP should, if possible, use its report as a public relations tool about the general issues around cancer and recruit Mr. Armstrong and knowledgeable speakers on each of the topics to present the report in New York with significant media coverage. Dr. Leffall responded that Mr. Armstrong has been an outstanding member of the Panel and still wants to help raise money for cancer research; he said that Mr. Armstrong likely would be willing to help with public relations, as he has devoted much of his life to promoting cancer awareness.

Dr. Runowicz commented that, relating to environmental issues, Dr. Jim Holland had performed relevant work with the mouse mammary tumor virus (MMTV), finding that breast development happens *in utero* and in the teenage years, so if the mouse mammary tumor virus is acquired at 13 years of age, cancer may develop when the patient is 40 to 60 years old. It would be difficult to track but useful to know whether a patient had been exposed to MMTV during the developmental years. The same idea

applies for ovarian cancer. The ovaries are exposed to the outside world, and in the future environmental or infectious or inflammatory associations with primary peritoneal and ovarian cancer may be evident.

Dr. David Abrams, Director, Office of Behavioral and Social Sciences Research (OBSSR), OD, NIH, noted that because of the report's emphasis on clinical patients as well as factors that have a big impact on cancer, Mr. Armstrong also would be an ideal person to send out messages about cancer's relationship to vulnerable lifestyles and environment. He added that 40 to 60 percent of cancer, particularly those attributable to tobacco smoke, would be drastically reduced if people stopped exposing themselves to extracellular pathogens. Dr. Abrams encouraged the NCAB and PCP to consider the balance in reducing cancer through social, ecologic, and lifestyle interventions as well as biomedical interventions. Dr. Chen suggested that the PCP should link its upcoming work on the environment with the idea of healthy lifestyles.

XIV. ANNUAL TOBACCO CONTROL UPDATE—DRS. CATHY BACKINGER, DOROTHY HATSUKAMI, AND SHU-HONG ZU

Tobacco Control Update. Dr. Cathy Backinger, Chief, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences (DCCPS), explained that the decrease in smoking in the United States stalled from 2003 to 2006 in adults, and there was an increase in smoking among high school students during this same time period. This means that about one of five adults in the United States smokes, and the prevalence among youth is approximately 23 percent, with 46.2 percent having tried smoking by the 12th grade. The number of states that require smoke-free workplaces and restaurants in the United States increased from 14 in January 2007 to 21 in January 2008. Secondhand smoke exposure fell by 70 percent between 1991 and 2002, but 43 percent of nonsmokers are still exposed, as are approximately 60 percent of children and approximately 30 percent of indoor workers.

There is concern that the use of smokeless tobacco may increase as cigarette companies have expanded into selling smokeless tobacco products. There is also concern because cigarette companies increasingly market cigarette alternatives such as tobacco pouches, modified cigarettes, tobacco lozenges, water pipes, and cigarette heating systems. The NCI collaborated with various government agencies and other organizations as part of the Youth Tobacco Cessation Collaborative to produce a special issue of the *American Journal of Public Health* (August 2007), and is also involved in other scientific collaborations. One collaboration is the U.S. Public Health Service Clinical Practice Guidelines entitled *Treating Tobacco Use and Dependence*. The NCI is participating on a 27-member panel that is revising the guidelines, which are forthcoming in May 2008. The guidelines continue to be the definitive source on providing the evidence base to clinicians on how to help their patients and clients quit smoking.

Dr. Backinger next introduced the two guest speakers for the session: Drs. Dorothy Hatsukami, Director, Transdisciplinary Tobacco Use Research Center, University of Minnesota; and Shu-Hong Zhu, Professor of Family and Preventive Medicine at the University of California at San Diego.

Science and Future Research Directions for Reduced Nicotine Content Cigarettes. Dr. Hatsukami explained that the study of reduced nicotine content cigarettes is important because nicotine is the addictive agent in tobacco products and is responsible for the development of addiction and difficulty in cessation. The dose of nicotine to establish and maintain addiction has been estimated to be approximately 5 milligrams per day. An article published in 1994 in *The New England Journal of Medicine* proposed a gradual reduction in the levels of nicotine in cigarettes over the course of 10 to 15 years to prevent nicotine addiction, especially by youth. Concerns raised with this proposal include: compensatory oversmoking; the black market sale of higher nicotine cigarettes; the fact that low-nicotine

cigarettes could serve as an appealing "starter product" for nonsmokers; and the lack of science to determine the feasibility of this approach. However, recent studies are beginning to address some of the critical questions associated with this public health approach.

A recent study (Benowitz et al, *Cancer Epidemiology Biomarkers and Prevention*, November 2007) addressed the safety of having smokers use progressively reduced nicotine content cigarettes and the effects of these cigarettes on consumer acceptability, lowering nicotine addiction, and promoting smoking cessation. The study found that a gradual reduction in nicotine content in cigarettes results in a progressive reduction in nicotine exposure, with little evidence of smoking compensation, and no evidence of increased exposure to toxicants or evidence of adverse effects of cardiovascular biomarkers. Additionally, these reduced nicotine content cigarettes are acceptable to smokers, even though the study participants still preferred their regular brands. At the end of the study, there was a significant reduction in participants' tobacco dependence scores, and surprisingly, 25 percent of the subjects achieved abstinence at 4 weeks after the study even though they were not intending to quit in the immediate future when they entered the study. The researchers concluded that the use of a nicotine-reduction strategy to prevent or reduce the level of nicotine addiction appears to be safe and feasible in the short term, but long-term studies are needed.

An additional study conducted by Dr. Hatsukami examined the effects of reduced nicotine content cigarettes in a population that wanted to stop smoking. The research found that de-nicotinized cigarettes reduced dependence, facilitated abstinence, and reduced toxicant exposure. Importantly, however, the investigators did not find a change in the perceived risk of disease compared to their usual brand cigarettes. The results from both these studies suggest that reduced nicotine content cigarettes have promise as a policy measure and as a smoking cessation tool, but more research is needed.

Tobacco Quitlines. Dr. Zhu explained that a quitline provides telephone counseling for tobacco cessation, which is more accessible to smokers than face-to-face counseling, and provides more opportunity for interventionists to be proactive. In California, the quitline is a centralized operation, with multilingual services and extended hours, which handles a large volume of calls and thus has strong implications for research and dissemination. A significant problem in any behavioral treatment is the attrition rate, because many people attend a single counseling session and then never return. Dr. Zhu's study showed that proactive counseling reduces the attrition rate by one-half. This switch to calling the smoker versus waiting for the smoker to call has dramatically improved the program's adherence and success rates.

The NCI's Cancer Information Service (CIS) was the first group to provide a cessation service via the telephone in the 1980s. In 1992, California established the first state quitline, the California Smokers' Helpline. Massachusetts set up its quitline in 1994 and Arizona in 1995. Many other states soon set up their quitlines. The Interagency Committee for Smoking Health, chaired by the U.S. Surgeon General, recommended in 2003 that a national quitline network be established. In 2004, the NCI and CIS coordinated a telecommunications system for a national quitline network, 1-800-QUIT-NOW, to serve as a portal to all state quitlines. This federal initiative also included efforts to help those states that did not have quitlines at the time. Currently, all states have quitlines and they collectively serve approximately 400,000 smokers per year, and 1-800-QUIT-NOW calls passed the 1 million mark in 2007.

Dr. Zhu described using the California Smoker's Helpline as the basis for several randomized trials. The first trial convinced the California state health department to provide funding for the service. In it, 3,000 smokers were randomized into three groups, with those who used only self-help to quit as the control group, along with single and multiple counseling groups. Those who received a single session did better than those using self-help, and those who received multiple sessions achieved the highest quit rate.

Later, a second trial conducted in the context of a statewide quitline service replicated the results of the first trial. Four subsequent trials targeted: nicotine replacement therapy users, teen smokers, pregnant smokers, and Asian-speaking smokers. Current and upcoming intervention research will involve smokers with co-morbidities such as depression, smokers who are proactively recruited via their doctor's offices, and nonsmokers who will serve as an extension of the quitline to help smokers quit. Further work will include collaboration with health care providers, to motivate them to encourage their patients to quit smoking and to refer their patients to quitlines for more extensive counseling service.

The role of quitlines goes beyond just providing cessation service, but to work with other tobacco control elements in the states: the mass media campaign, the worksite policy changes, the health education programs in the school system, and the health care providers. The quitlines have been able to reach underserved populations and they should be leveraged to facilitate other tobacco control activities to achieve a greater population effect.

Questions and Answers

Dr. Chen asked about the NCI's involvement in the national quitline and the effectiveness of the statewide quitlines around the country with NCI support. Dr. Backinger responded that all the state lines have an evaluation component and collect data about the quit rates. Ms. Mary Anne Bright, CIS, explained that the network was established by charge of Tommy Thompson, then Secretary of the DHHS. The process evaluation, which interviewed 142 stakeholders, demonstrated that the collaborative nature of this work was a success. She added that it would be useful to do an evaluation of the quit rates and the services offered, which vary among states.

Dr. Karen Meneses, Professor and Associate Dean for Research, University of Alabama at Birmingham School of Nursing, asked about the characteristics of subjects in the studies on young adults, and commented that actual interventions used in the studies in terms of reduction of smoking and lozenges are similar to those that the tobacco companies are using to encourage smoking. Dr. Hatsukami responded that in her study, the population tended to be middle-aged. In terms of the use of nicotine lozenges or reduced nicotine content cigarettes, this study tried to use these products to wean participants off tobacco products, which is quite different from what the tobacco companies are doing. Dr. Meneses commended the focus on pregnant smokers and those who accepted counseling via the quitline.

Dr. Anthony Atala, Director, Wake Forest Institute for Regenerative Medicine and Professor and Chairman, Department of Urology, Wake Forest University School of Medicine, asked if there were plans to compare the nicotine reduction to other interventions in a randomized prospective study, noting that participants might begin chewing nicotine gum. Dr. Hatsukami responded that it will be important to compare de-nicotinized cigarettes with common conventional treatments for smokers, and to examine their use in conjunction with pharmacotherapies. The use of de-nicotinized cigarettes targets a different aspect of tobacco addiction, a sensory component that often has been neglected, but may be just as important in terms of maintaining the addiction to cigarettes.

Dr. Von Hoff asked whether there was a way to verify if those participants who said they quit smoking with the help of the quitline actually did quit. Dr. Zhu responded that in the earlier trials, volunteers went to the participants' homes to collect saliva samples for cotinine tests. In the later trials, because the misreporting rate is very low, participants were asked to send a saliva sample by mail. It is fairly well accepted that if the intervention is of low intensity, the misreporting rate is low.

Dr. Chabner noted that not much has been accomplished if only 1 percent of smokers are reached and only 20 percent of those people abstain in the long run. A better overall strategy to promote smoking

cessation is needed. Dr. Backinger responded that a large part of the problem is a lack of funding. States could not handle more callers to their quitlines, because there are not enough counselors. Dr. Chabner asked about the cost for each person who quits and stays off cigarettes by using the quitline. Dr. Abrams responded that using standard qualities, for quality-adjusted life years saved, most of the medium-level-intensity smoking programs cost between $1,000 and $5,000 per quality, compared to other palliative interventions. For example, managing high blood pressure or cholesterol runs in the range of $12,000 to $25,000 per quality. These numbers are in life years saved rather than the cost to the quitter, the latter varying by the intensity and cost of specific programs.

XV. ANNUAL REPORT: IMPLEMENTATION OF CLINICAL TRIALS WORKING GROUP/TRANSLATIONAL RESEARCH WORKING GROUP (CTWG/TRWG) RECOMMENDATIONS AND CLINICAL TRIALS ADVISORY COMMITTEE (CTAC) STATUS REPORT—DRS. SHEILA A. PRINDIVILLE, KENNETH H. BUETOW, JAMES H. DOROSHOW, AND LYNN MATRISIAN

CTWG and TRWG Implementation Update: Integrated Management. Dr. Prindiville explained that the CCCT manages the implementation of CTWG initiatives with internal oversight provided by the Clinical Trials Operations Committee (CTOC). The CTAC provides extramural oversight of NCI's clinical trials enterprise. The CTAC has four subcommittees, two of which are active, and two (the Evaluation Subcommittee and the Operational Efficiency Working Group) that are in formation. The Ad Hoc Coordination Subcommittee is working to harmonize NCI's clinical trials program guidelines among Cancer Centers, SPOREs, and Cooperative Groups to make them consistent, and determine how to integrate TRWG initiatives and CTWG initiatives into the operations of the CTAC. The Ad Hoc Public-Private Partnership Subcommittee advises on enhancing clinical trials through collaborative interactions with the private sector, such as standardization of clinical trial agreement terms.

In terms of scientific prioritization of clinical trials, the CTWG recommended that the NCI develop an Investigational Drug Steering Committee (IDSC) to provide input on the development of early phase trials, and a Disease-Specific Steering Committee (DSSC) system to evaluate and provide input for Phase III trials. The IDSC has been in operation for more than 1 year, and has formed several task forces in the areas of signal transduction, biomarkers, angiogenesis, and clinical trial design. The IDSC has been increasing transparency in the NCI development processes, providing strategic review of NCI's early phase clinical trials, and enhancing scientific input for novel therapeutics. The responsibilities of the DSSCs are to: prioritize large Phase II trials and all Phase III concepts for therapeutic clinical trials, convene state-of-the-science meetings to help the NCI prioritize strategies, develop Phase II and III concepts for new clinical trials, and periodically review accrual and unforeseen implementation issues for approved concepts. The current committees are Gastrointestinal Cancer, Gynecological Cancer, Head and Neck Cancer, and Symptom Management and Health-Related QOL. The CTWG report called for the full implementation of all disease committees by the end of 2010. A Genitourinary Cancer Steering Committee is being formed now, and the Lung Cancer and Mesothelioma Steering Committee also will be formed this year. In addition, there will be a Patient Advocate Steering Committee; the remainder of the committees will be formed in FY 2009 and 2010. Another CTWG prioritization and scientific initiative called for establishment of a funding mechanism and prioritization process to ensure that the most important correlative science and QOL studies can be initiated in a timely manner in association with the clinical trials. The primary purpose is to fund studies conducted in association with Phase III trials when the cost of the studies is too large to be covered by the Cooperative Group mechanism. Prioritization criteria have been developed and standards for the assays to be used in those correlative marker studies are being developed. The program for FY 2008 will be funded via administrative supplements through the Cooperative Group program as well as the CCOP research bases, with up to $5 M available. These studies will be reviewed by scientific steering committees and CTEP and Division of

Cancer Prevention (DCP) staff, who will make recommendations to the CTOC. In addition, the CTAC will review the portfolio and provide final funding recommendations during its June 2008 meeting.

NCI Clinical Trials Database Implementation Plan. Dr. Kenneth H. Buetow, Director, Center for Biomedical Informatics and Information Technology, NCI, described four related informatics-associated initiatives associated with CTWG. These include: the development of a clinical trials database; the reconciliation and development of a National Clinical Trial Information Technology Infrastructure system that is fully interoperable with caBIG™; the development of standardized case report forms; and the development of a repository of investigator and site credentials that is recognized and accepted by the NCI, industry sponsors, clinical investigators and clinical trial sites. The clinical trials database serves as a single source for access to transparent information about NCI-supported trials. The first step of this process is the registration of these trials along with consent and Institutional Review Board (IRB) approval documents. The NCI Clinical Trials Data Portal is in place and currently in the testing phase. The resulting reports are similar in content to the NCI Cancer Centers' Summary 4 reports. The CTWG's last charge for this project is making the information available to the general public and the NCI.

Implementation will begin with the assembly of NCI policy implementation teams to address abstraction and quality control issues. This system is designed as a process for trials that are not already reporting into CTEP or DCP, such as those conducted by Cancer Centers, SPOREs, P01, or R01 grants. Reporting already done through CTEP or DCP will be visible through this infrastructure. At this time, reporting is required for interventional trials only, with NCI-sponsored trials reported at the principal investigator (PI) level and non-NCI-sponsored trials reported at the site level. As of January 1, 2009, all new trials will be reported within 21 days after activation, with all active trials to be entered by June 2009. Starting in July 2009, quarterly reporting of all trial updates and accrual information will be required.

Because many organizations need preparatory time, the project started in January 2008. The NCI is creating educational documents and informational Web sites for grantees, and will pilot the process at 5 to 10 sites starting in July 2008. The next version of the database, which will require outcome reporting, will begin a pilot in January 2010. Adverse effects and outcomes must be reported to the NIH as mandated by Public Law 110-85, the FDA Amendments Act. All clinical trials need to be reported as of December 2008 at www.clinicaltrials.gov per statutory requirement; because of the CTWG's initiatives, however, the NCI already is meeting this goal and is positioned to help lead the agenda for NIH clinical trials reporting.

Activating and Opening Oncology Clinical Trials: A Process and Timing Study. Dr James H. Doroshow, Director, Division of Cancer Treatment and Diagnosis, NCI, updated the NCAB on CTWG recommendations regarding operational efficiency and an evaluation system for clinical trials. He began with a presentation by Drs. David Dilts and Alan Sandler, Vanderbilt University, which had previously been presented to the CTAC. To gather data, they asked sites what steps are taken to activate a clinical trial, compare the responses to the policies and procedures manuals at those institutions, and then compare this to what actually occurs in the initiation of a trial. The results show that, at three different Comprehensive Cancer Centers, it takes approximately 200 steps to activate an investigator-initiated trial. For Phase III cooperative group trials, it takes an average of 800 days from the initial study idea to the time that the study is ready to be initiated, and takes another 3 to 6 months to begin the trial. The median number of days from concept to trial for investigator-initiated trials is 211 to 451 at the Comprehensive Cancer Centers with the best clinical trials systems. A study might not be relevant if it takes 3 years to open. Another issue is the accrual of patients for these trials, which remains the same in this example whether pediatric trials are included or excluded. Between 50 and 60 percent of all the trials entered in

these Cancer Centers accrue fewer than five patients, and approximately one quarter accrues no patients. In 15 Eastern Cooperative Oncology Group (ECOG) trials, those that took in excess of the median number of days to open never completed their accrual. Dr. Dilts made the following recommendations for immediate improvement, which will be evaluated by CTWG, in response to these findings: immediately start collecting and analyzing data; eliminate entitlement culture by refusing to fund some trials; do not allow investigators to make changes to their studies once they have moved through the IRB; and once policies and procedures are instituted, the NCI must adhere to them. A simulation was conducted to estimate the effect of doubling the budget of one of the cooperative groups to allow for more staff. This would only change the mean time for the study activation minimally, but improving review time as well as doubling the budget does have a significant effect. This clearly is a system-wide problem that will require major changes. Long-term recommendations are to develop standard administrative processes and use focused Phase III teams. The next steps to take in creating operational efficiency are to study the intramural program, develop a working group, and cut clinical trial activation time in half to remain competitive internationally.

CTWG Evaluation Plan Results of Baseline Feasibility Analysis. Dr. Doroshow explained that a systematic evaluation of the NCI clinical trials system was needed because prior evaluations did not integrate qualitative and quantitative information. A full evaluation also would establish a structured framework for continuous monitoring and feedback for mid-course corrections. The CTWG recommended that experienced evaluation specialists perform a feasibility baseline analysis and periodic evaluation as CTWG implementation proceeds. The evaluation should compare the baseline to the future based on system outcome measures (overall output) and system performance measures (performance of individual CTWG initiatives.) The system outcome measures gauge the quality and impact of trials and the efficiency of both trial development and initiation and trial conduct.

Data were gathered through interviews, database analyses, and document reviews. Baseline interviews were conducted with 81 individuals including NCI staff, trialists, and Cooperative Group members. In addition, an expert panel helped to develop measures and interview guides. In terms of quality of trials, the CTWG examined whether publications from the NCI-sponsored trials were captured; approximately 50 percent of trials over 4 years resulted in publications, and these were difficult to find. One recommendation was to provide a field for reporting publications so that the publication rate and types of publications that emanate from these studies can be used as a quality measure. To measure the impact of the trials, though arduous, it would be useful to go back to National Comprehensive Cancer Network (NCCN) guidelines and determine which trials changed clinical practice, because this is a very pertinent outcome measure. Regarding the CTWG coordination initiatives, the baseline study reported almost no incentives in the NCI Award guidelines to promote collaborations among Cancer Centers and none for P01 grantees, but strong incentives exist for collaborations across Cooperative Groups and SPOREs. Regarding the CTWG prioritization initiatives, a number of Phase I and II investigators were interviewed about their perceptions of the system. Perceptions of the Cancer Therapy Evaluation Program (CTEP) Clinical Development Plans were highly variable, the pre-IDSC process was viewed as not transparent, and the pre-IDSC trial quality had mixed results. Comments on the level of transparency of the CTEP prioritization process varied, and the quality of the Clinical Investigations Branch trial concepts was perceived as mixed.

The efficiency of Phase III trials was low in terms of accrual. An analysis of 150 Phase III trials at 1,516 accruing institutions showed that two-thirds accrued fewer than five patients per site per trial. Two-thirds of all patients come from 16 percent of the institutions. The next steps for the evaluation plan involve: developing a specific plan for future evaluation; refining baseline measures and developing protocols for future measures; incorporating additional information in clinical trials databases to

strengthen future evaluation efforts; preparing initiative-specific timelines for future evaluations; and formation of a CTAC subcommittee to oversee the evaluation process.

TRWG Report Implementation. Dr. Matrisian presented information on the TRWG report "Transforming Translation: Harnessing Discovery Research for Patient and Public Benefit." The TRWG began by building the structure to integrate the various aspects of the NCI that are involved in translation research. The plan involves expanding the mission of the CTAC to become the Clinical and Translational Advisory Committee, expanding the mission of the internal NCI clinical trials operating committee to involve translational research, and building on the resources within the Coordinating Center for Clinical Trials to encompass the duties that were assigned to the translational research support office. The CTAC will need additional members with translational research expertise to assume this role. Additionally, the operating committee will require added representation from the Division of Cancer Biology and the Office of Technology and Industrial Relations and will cover TRWG as well as CTWG issues at its meeting. The Coordinating Center for Clinical Trials has started the process with Dr. Matrisian's half-time effort, and will require additional staff. The action items are to modify the charter, add members to the CTAC, and to expand the Coordinating Center. Future initiatives will examine how the coding system within the NCI can identify grants as translational and create a prioritization process to identify those ideas that are ripe for translation, give them necessary resources for development, and modify some of the award guidelines to include characteristics, identified by the TRWG, that help accelerate the translational research process.

Questions and Answers

Dr. Niederhuber commended the CTWG baseline evaluation analysis; the data and evidence will allow the NCI to make some real changes. The Institute of Medicine (IOM) will work with the NCI and support needed changes, which can result in enormous cost savings. The integration of translational research into the CTWG report and implementation strategies is important.

Dr. Chabner commented that this information was crucial to the mission of the NCI, and that many of the insights are applicable to clinical trials with which he is involved. He added that, based on his experience, the pediatric Cooperative Groups do contribute to the low accrual statistics. Cooperative group trials are given lower priority than Phase I and Phase II trials. In terms of the analysis of trial activation, in his institution it takes 100 to 120 days to review a trial, and it took an equal amount of time to activate it in the past for two reasons: everything was conducted in a linear fashion rather than in parallel, and the trial was not activated as it went through the review process. The latter has changed, and now many of the necessary steps are completed before the trial has finished review. Finally, it is not sensible to repeat, at an institutional level, the review of biostatistics and other reviews done at the NCI. It would be helpful if the NCI could produce some guidelines that would aid in eliminating repetitive reviews. Dr. Niederhuber responded that the pressure that Cancer Centers are under to have trials for rare cases, even though they may only accrue two patients in a year, should be considered as another factor in the low accrual rates found by the study. Dr. Atala expressed surprise at the length of trial activation time, and noted that it may be due to the amount of duplication in the process, including at the IRB level, instead of the fault of the FDA and other agencies. National parameters for expediting these processes would be useful.

Dr. Coffey commented that the information in the presentations was profound, and required more discussion than time would allow. He strongly urged the NCI to situate the SPORE program elsewhere within the NCI than in the DCTD, given the DCTD's monumental tasks associated with the CTWG and TRWG recommendations. Drs. Niederhuber and Doroshow provided reassurance that the SPORE program will receive ample attention by the NCI leadership, and that SPORE investigators will be provided the opportunity to participate in the decisionmaking process through the work of steering

committees. The NCI will use the knowledge based in the SPOREs to advance the entire national program in clinical trials research; the DCTD is overseeing the NCI's work in translational research, and the SPORE program consequently will be able to exert special influence by residing in the DCTD.

Dr. Von Hoff suggested that more young investigators should be included in the DSSCs. Dr. Doroshow agreed, and added that many of the task forces are led by associate professors. Dr. Von Hoff suggested that researchers should be approached at a younger age. He added that the ASCO has a program called "Just in Time" in which patients instantly are matched with trials seeking participants with the same illness, which helps increase the accrual rate. The trial can be preapproved, and that way the NCI can open it in a single day. Dr. Runowicz noted that more discussion was needed on the topics raised in the presentation, and that the issues will be revisited at the June NCAB meeting. Dr. Niederhuber added that the project likely would take several years to complete, and that the advisory boards would be updated during the process.

XIII. 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 145th regular meeting of the NCAB was adjourned at 11:30 p.m. on Wednesday, February 6, 2008.

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

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