DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
141st NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
February 6, 2007

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 141st regular meeting on Tuesday, 6 February 2007, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, 6 February 2007, from 8:00 a.m. to 3:30 p.m. The meeting was closed to the public from 3:45 p.m. until adjournment at 5:00 p.m. NCAB Chair Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, Farmington, CT, presided during both the open and closed sessions.

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

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

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

Members, Executive Committee, National Cancer Institute, NIH

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

Liaison Representatives

Ms. Carolyn Aldige, Cancer Research and Prevention Foundation
Dr. Eve I. Barak, National Science Foundation
Ms. Paula Bowen, Kidney Cancer Association
Mr. William Bro, Kidney Cancer Association
Dr. Carol Brown, Society of Gynecologic Oncologists
Ms. Paula K. Brown, Intercultural Cancer Council
Mr. Rodney Cotton, American Urological Association
Mr. George Dahlman, Leukemia and Lymphoma Society
Ms. Nancy Riese Daly, American Society of Clinical Oncology
Ms. Georgia M. Decker, Oncology Nursing Society
Dr. Margaret Foti, American Association for Cancer Research
Dr. Robert W. Frelick, Association of Community Cancer Centers
Ms. Ruth Hoffman, Candlelighters Childhood Cancer Foundation
Dr. Lovell A. Jones, Intercultural Cancer Council
Ms. Rebecca A. Kirch, American Cancer Society
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. Christy Schmidt, American Cancer Society
Ms. Susan Silver, National Coalition for Cancer Survivorship
Dr. John Stevens, American Cancer Society
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Mr. Douglas Ulman, National Cancer Institute, Director's Consumer Liaison Group
Dr. Robyn Lynn Watson, American Society of Therapeutic Radiology and Oncology
COL (Ret.) James E. Williams, Jr., Intercultural Cancer Council
Dr. Stanley Zinberg, American College of Obstetricians and Gynecologists

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I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF 30 NOVEMBER–1 DECEMBER 2006 MINUTES—DR. CAROLYN D. RUNOWICZ

Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, Farmington, CT, called to order the 141st NCAB meeting. She welcomed members of the Board, the President's Cancer Panel, *ex officio* members of the Board, staff, and guests. She introduced and welcomed new member to the Board Dr. Anthony Atala, Director, Wake Forest Institute for Regenerative Medicine, and Chairman, Department of Urology, Wake Forest University School of Medicine. Members of the public were welcomed and invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), in writing and within 10 days, any comments regarding items discussed during the meeting. Dr. Runowicz reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Motion. A motion was made to approve the minutes of the 30 November–1 December 2006 NCAB meeting. The motion was seconded and the Board unanimously approved the minutes.

II. FUTURE BOARD MEETING DATES—DR. CAROLYN D. RUNOWICZ

Dr. Runowicz called Board members' attention to future meeting dates, which have been confirmed through 2008.

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

Dr. John Niederhuber, Director, NCI, welcomed NCAB members and noted that the Revised Continuing Appropriations Resolution (CR) passed recently by Congress and the release of the Fiscal Year (FY) 2008 President's Budget has made it necessary to present another budget update, even though the NCI budget had been the focus of the day-long Executive Council retreat in January attended jointly by the NCAB, Board of Scientific Advisors (BSA), and Boards of Scientific Counselors (BSC).

Budget Update—FY 2007 and FY 2008. Members were reminded that NCI planning since the previous spring has been based on the President's FY 2007 Budget, which decreased by $36.45 M from FY 2006 appropriation, taking into account also the mandated taps, utilities, and the NIH Roadmap, which increased the deficit to about $122 M. An intensive portfolio review by the Executive Committee (EC) identified about $175 M in reductions and phaseouts to cover the deficit and create a pool of about $60 M in excess of the projected $122 M deficit. Dr. Niederhuber noted that the EC has created a prioritized list of new initiatives and previously reduced existing projects to be considered for funding from that pool, as well as additional items that will be considered if funds become available. He then reminded members of the trans-NIH guidelines for developing an FY 2007 operating budget to be implemented across the NIH under a full-year CR if that should be enacted: no inflationary adjustments on noncompeting (Type 5) grants and a decrease of about 3 percent from commitments of record for all grants; a mandate that the same number of competing Research Project Grants (RPGs) be awarded by the NIH in FY 2007 as were awarded in FY 2005 (about 9,600), with a particular emphasis on new investigators; and an average cost of competing RPGs set at the same figure as in the FY 2006 budget.

On January 31, a revised CR was passed by the House of Representatives providing $28.9 B for the NIH in FY 2007, an increase of $620 M over FY 2006. Joint action by the House and Senate is expected before the expiration of the current CR on February 15. Dr. Niederhuber reviewed the revised CR provisions: 1) a Common Fund, which now includes the NIH Roadmap, is set in the NIH Office of

the Director (OD) at $483 M; 2) Institutes and Centers (ICs) receive no specific increases but retain funds previously earmarked for the NIH Roadmap as well as funds that were transferred to the Center for Medicare and Medicaid Services (CMS) in FY 2006 ($267 M total); 3) the NIH will receive funds to pay partially for the 2007 Cost of Living Allowance (COLA) increases for Federal salaries; 4) the NIH is to fund 500 more RPGs; 5) 1,500 new investigator awards are to be made NIH-wide; and 6) ICs are to fund additional RPGs with one-half of the money that they retain from the Roadmap. A breakdown of total adjustments (new dollars plus transfers within the NIH) in the revised CR reveals Congressional interest in protecting young scientists and new investigators, funding new activities within the NIH OD related to implementing the reauthorization bill, and helping to defray the rising costs within the National Center for Biological Information (NCBI) for data acquisition related to NCI genome projects.

For the NCI, FY 2007 appropriations as approved by the full House in the revised CR would be $4,793,356, a $46.127 M increase over FY 2006 because the CMS transfer and Roadmap tap would be restored. In regard to NCI RPGs, Dr. Niederhuber reminded members that a target of 1,280 competing grants (for $415,067 M) had been reached by the end of FY 2006. Competing RPG numbers under the FY 2007 annualized CR were estimated at 1,244 grants for $403,280 M. Under the FY 2007 revised CR approved by the full House, the estimate would be 1,310 competing grants for a total of $424,697 M. For comparison, Dr. Niederhuber pointed out that a payline at the 12th percentile and success rate of 19.4 percent were reached in FY 2006. Estimates for FY 2007 under an annualized CR would be a payline at the 11th percentile and success rate of 18 percent. Under the FY 2007 revised CR, the payline would be estimated at the 12th percentile and the success rate at 18.9 percent. Members were reminded that the payline and success rate could change because they are influenced by the denominator, and the number of grants received continues to increase. Dr. Niederhuber gave assurance that NCI grant awards would be driven by science, not target numbers, and that an attempt would always be made to identify funding for good science.

In the recently released President's FY 2008 Budget, the request for the NIH is $28.849 B, an increase of $232 M (0.8 percent) over the FY 2007 annualized CR and including a $72M increase for the NIH Roadmap for a total increase of $486 M. The President's Budget request for the NCI is $4.782 B, a $9 M decrease (-0.2 percent) from the FY 2007 annualized CR. Dr. Niederhuber reminded members that the House-approved revised CR calls for a single appropriation for the NIH and that possible changes resulting from the recently enacted reauthorization legislation are not yet known. He pointed out that, until a new approach to budget development is indicated, the NCI will put together its FY 2008 budget based on past operations in relation to the NIH, Office of Management and Budget (OMB), Department of Health and Human Services (DHHS), and the White House.

President Bush's Visit to the NIH. Dr. Niederhuber reported a positive reaction by the President on his recent visit to the NIH. In planning meetings prior to the visit, a strong cancer focus had been requested; therefore, the President met with Dr. Niederhuber, toured NCI laboratories, and visited with NCI patients and staff. Arrangements were made for the President to announce the latest mortality data from the American Cancer Society (ACS), which showed a continuing decline in cancer deaths since 2003, reflecting the success of efforts in the National Cancer Program. The data were generated by the NCI's Surveillance, Epidemiology, and End Results (SEER) Program.

NIH Reform Act of 2006. The third reauthorization in NIH history and the first in 14 years was signed by the President on January 15, 2007. Key provisions included the creation of a Division of Program Coordination, Planning and Strategic Initiatives (DPCPSI); Common Fund; Council of Councils with oversight responsibility; and Scientific Management Review Board. Other elements of the Act related to the authorization of appropriations, reorganization, and reporting requirements. Dr. Niederhuber noted that NIH staff have been comparing the old and new authorization bills and creating a

work assignment list for the implementation. An *Ad Hoc* Working Group of the NIH Steering Committee has been established, chaired by Dr. Raynard Kington, NIH Deputy Director, to conduct a detailed analysis of the Reform Act of 2006 and propose plans for its implementation. The Group is composed of IC Directors and NIH OD leadership in legislation, policy, management, communications, extra- and intramural activities, budget, and the Office of the General Counsel. Seven Implementation Groups have been formed, the majority headed by IC Directors. Dr. Niederhuber will head the Reporting Group. Regular joint meetings of the Implementation Groups will ensure input across all ICs and Centers into the activities of each area. Finally, Dr. Niederhuber announced that Dr. Alan M. Krensky, formerly of the Stanford University School of Medicine, has been named the NIH Deputy Director of the Office of Portfolio Analysis and Strategic Initiatives (OPASI). Dr. Krensky also has accepted a position in the NCI intramural program and will have a laboratory in Building 37.

Reorganization of the NCI OD. Dr. Niederhuber briefly reviewed the results of the reorganization of the NCI OD, which has been underway since August 2006, with the help of the EC. The changes reflect the attempt to streamline the structure according to affinities of activity and to realize some savings. One example of this is the new Office of Communications and Education, which combines the former Office of Communications and the Office of Education. A small Office of Media Relations has been established and is tied closely to the Director. A search is in progress for a new Executive Officer.

Clinical Trials Advisory Committee (CTAC). The CTAC was established in response to the Clinical Trials Working Group (CTWG) recommendation that an extramural oversight committee be formed to advise the NCI Director on clinical trials. Chaired by the NCI Director, the CTAC includes 10 members who hold concurrent membership on the NCAB, BSA, BSCs, and Director's Consumer Liaison Group (DCLG), and 14 members who represent the broad clinical trials community. Members were reminded of the significant clinical trials infrastructure that is in place across the nation, with 1,878 sites that have patients enrolled in open trials (based on 2004 data). The NCI's Clinical Trials Cooperative Group Program is distinctive among NIH-supported clinical trials programs: 1) the infrastructure is continuously available to test new therapeutic strategies; 2) it consists of researchers at institutions affiliated with the Groups who jointly develop and conduct trials in multi-institutional settings across state boundaries; and 3) its flexible research agenda allows change of strategy in response to changing scientific opportunities and new discoveries.

Dr. Niederhuber concluded by stating that the future depends on working as an Institute through a continuum of science that comprises three research spaces: biology of cancer, chemistry, and translation. He called attention to the trans-NCI Clinical Imaging Program, which is focusing on research in the submolecular space. The program has research and service components and features both molecular and functional imaging, profiling, and therapy. Research is being conducted on campus in the area of three-dimensional, high-resolution electron microscopy, and imaging is incorporated into the majority of clinical trials in the NCI's Center for Cancer Research (CCR). The program also engages industry in a partnership for the technology development. As examples of what is possible with submolecular imaging, Dr. Niederhuber showed 3-D images of Simian immunodeficiency virus and the interior of a single MNT-1 melanoma cell at 30 nm resolution. In closing, Dr. Niederhuber emphasized that, although there are currently more scientific opportunities than available resources, good management of the significant resources appropriated to the NCI is important, as well as finding ways to leverage those resources by working with the private sector in some areas, especially technology development.

Questions and Answers

Ms. Kathryn Giusti, CEO and Founder, Multiple Myeloma Research Foundation, Inc., asked whether there had been an opportunity during the President's visit to communicate the continuing monetary and overall barriers faced in cancer research and drug development. Dr. Niederhuber described the topics addressed at a roundtable discussion. These included concerns about patients' rights and risks as they relate to genetic information in The Cancer Genome Atlas (TCGA) project expressed by Dr. Francis Collins, Director, National Human Genome Research Institute (NHGRI); living in a family with the BRCA-1 risk factor and a history of cancer as related by patient representatives; and a review of NCI research to identify the abnormal genes responsible for breast and prostate cancer, as well as plans for pancreatic cancer research. Dr. Donald Coffey, Professor of Urology/Oncology/Pathology/Pharmacology and Molecular Science, Johns Hopkins University School of Medicine, pointed out that the public and patient advocates have a role to play in asking the challenging questions of Congress. Dr. Bruce Chabner, Clinical Director, Massachusetts General Hospital Cancer Center, asked about the extent to which Congress perceives that the Roadmap initiative will provide extra funding so that researchers also will benefit from the investment, in a time of flat budgets. Dr. Niederhuber expressed the view that Congress sees the Common Fund as an enabling fund or incubator space for innovation. He reminded members that the NCI and cancer community are involved in planning for the next generation of initiatives for the Common Fund, which include proteomics, epigenetics, and the microbiome. He suggested that the take-home message for colleagues in the scientific community is that these deliberations are public and all have opportunities through the Web site to impact or have input into the decisions as to what is supported by the Common Fund. An agenda item could be included for the next meeting to present a summary of how the money is being spent.

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

Dr. LaSalle Leffall, Jr., Charles R. Drew Professor of Surgery, Howard University College of Medicine, reminded members that he had provided information at the previous NCAB meeting on two of the meetings in the 2006-2007 series entitled "Promoting Healthy Lifestyles to Reduce the Risk of Cancer." The first meeting on September 11 in Minneapolis, MN, examined how obesity, physical activity, and nutrition affect cancer risk. The second meeting in Lexington, KY, on October 23, focused on the effects of tobacco and environmental tobacco smoke on cancer risk. At both meetings the Panel gathered testimony on current research, knowledge gaps, and community programs relevant to promoting healthy behaviors and cancer risk reduction. He presented a report on a third meeting in the series, which took place in Portland, OR, on December 5, to continue the exploration of obesity, physical activity, and nutrition as they impact cancer risk. Presenters at this meeting emphasized the importance of community action to implement interventions known to be effective in promoting better nutrition, increased physical activity, and weight loss, particularly in light of the growing evidence base linking obesity to cancer risk. Support was expressed for a number of policies that have not yet been widely adopted. These include: 1) providing point-of-purchase nutrition information on fast-food chain and restaurant menus; 2) mandating daily physical activity in schools; 3) providing a better public understanding of body mass index (BMI) as a marker to measure risk of obesity; and 4) incorporating BMI as part of annual childhood and adult physical exams and as part of school health assessments.

From a research perspective, the Panel heard that evidence of increased risk for all cancers is strongly linked to weight. This finding may be because weight as a marker is easier to measure than effects of changes in diet or physical activity. There was reiteration and support of research findings linking obesity to endometrial, breast, and colon cancers and to increased risk of kidney and esophageal cancers. Additional insights were provided as to possible biological mechanisms related to the increased risk of these cancers. The Panel heard that body weight is believed to affect circulating levels of peptide

and steroid hormones as well as growth factor binding proteins. Scientists also are looking at adipose tissue as an endocrine organ that both produces hormones and receives signals that may be dysregulated as a result of obesity. New information presented in Portland suggested that excess weight and a high BMI may affect cancer prognosis in addition to cancer risk. In both pre- and post-menopausal women, excess weight appears to negatively affect breast tumor characteristics and treatment outcomes, leading to poor prognosis and decreased long-term survival. Presenters noted the gap in research on biological mechanisms linking energy balance (the variance between calories consumed and calories expended) and cancer and the role of energy balance in cancer survivorship. Presenters stressed that obesity is a critical public health problem impacting not just cancer but other chronic diseases and that the trend must be reversed, particularly among youth.

Community initiatives aimed at increasing physical activity among preschool and school-age children and addressing obesity through changes in the built environment were presented. The built environment encompasses all the buildings, spaces, and products created or modified by people. This is an area of increasing interest as it relates to nutrition, physical activity, and obesity. The Panel heard once again that decreasing obesity rates will require collaboration across multiple sectors of society and institutional action on many levels. In this regard, there is a need to better learn how to modify and impact the institutional behavior of schools, businesses, food industries, community development boards, and legislative bodies, among others.

On February 12, the Panel will hold its final meeting in this series in Jackson, MS. Additional issues related to the impact of tobacco and environmental tobacco smoke on cancer risk will be examined. Dr. Leffall concluded by calling attention to the flier, which was included in the meeting materials, describing the Panel's 2006-2007 meeting series and providing information on the three prior meetings.

Questions and Answers

Ms. Giusti commented on the success of Lance Armstrong, Member of the President's Cancer Panel, and Founder of the Lance Armstrong Foundation (LAF), in raising public awareness about cancer issues as evidenced by the response to his appearance with Clifton Leaf on Cable News Network (CNN). She asked if there is a way to build on his message and communicate to the President and Congress with more of a patient focus as to what the obstacles and problems really look like. Dr. Coffey agreed that having Mr. Armstrong as a spokesman for the cancer field is a positive thing, both for his status and drawing power as a public figure and for his ability to touch people as a patient. He suggested the need to build on those messages with the professional societies and to ensure that the message about scientific progress and opportunities is accurate. Dr. Niederhuber reminded members that Mr. Douglas Ulman, DCLG Chair, is also the President of the LAF and ensures that information about NCI is immediately available to the Foundation. Dr. Leffall agreed with the value of telling the patient story and emphasizing the role of patients.

V. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Policy Analysis and Response (OPAR), reminded members that the FY 2007 President's Budget was announced in February 2006, allocating $28.6 B for the NIH and $4.75 B for the NCI. The NCI has been operating under a CR since the end of FY 2006 on September 30, 2006. A long-term revised CR was passed by the full House on January 31, and Senate action is expected before expiration of the current CR on February 15. The FY 2008 President's Budget was announced on February 5. Ms. Erickson reported that no hearing date has been set for action in the Senate, but that the format will probably continue to feature Dr. Elias Zerhouni, Director, NIH, as principal witness, accompanied by IC Directors. In the House, the hearing date has been set for March 6 with Dr. Zerhouni as principal witness accompanied by the Directors of the NCI; National Institute of

Allergies and Infectious Diseases (NIAID); National Heart, Lung, and Blood Institute (NHLBI); National Institute for Child Health and Human Development (NICHD); and National Center on Minority Health and Health Disparities (NCMHD).

Congressional Visits. On December 14, 2006, Senator Edward Kennedy (D-MA) visited multiple ICs, including the NCI where he heard presentations from intramural program scientists on molecular diagnosis of cancer and the role that nanotechnology will play in the future of cancer diagnosis. On January 22, 2007, Representative Michael Castle (R-DE) visited the NCI and two other Institutes to hear about cancer, diabetes, and stem cell research. At the NCI, he heard a presentation similar to that heard by Senator Kennedy.

NIH Reform Act of 2006. Members were reminded that the NIH Reform Act was signed into law on January 15, 2007, with key provisions relating to organization of the NIH, a Scientific Management Review Board, authority of the NIH Director, authorization of appropriations, an NIH Common Fund, biennial reports of the NIH Director, and demonstration projects. An *Ad Hoc* Working Group, headed by Dr. Kington, is charged with completing a careful, detailed analysis of the legislation and proposing plans for its implementation that will aid the NIH in serving the public and scientific community more effectively. Ms. Erickson noted that implementation meetings are being held nearly nonstop, and an effort has been made to get maximum representation by the NCI in the various groups working on legislation, policy, management, communications, extra- and intramural activities, and budget. She called attention to a statement issued by Dr. Zerhouni expressing his stand on the NIH Reform Act: "This affirmation from Congress has come at a critical time, and we want to ensure that we take the best possible advantage of its promise. We will be communicating with the community regularly as we make progress in this process."

Outlook—110th Congress. Ms. Erickson commented that the 110th Congress in these early days has been focusing on the war in Iraq and concluding action on FY 2007 appropriations. She briefly reviewed the structure and leadership of committees relevant to the NIH and NCI. In the House, Representative Obey (D-WI) chairs both the Full Appropriations Committee and the Appropriations Subcommittee; seven new members are included. The Energy and Commerce Committee, chaired by Representative Dingell (D-MI), and the Health Subcommittee, chaired by Representative Pallone (D-NJ), have jurisdiction over authorization. Seven new members have joined these committees. Representative Waxman (D-CA) chairs the Government Reform Committee, which has oversight responsibility. In the Senate, Senator Byrd (D-WV) chairs the Full Appropriations Committee and Senator Harkin (D-IA) chairs the Appropriations Subcommittee. Two new members are included. The Health, Education, Labor and Pensions (HELP) Committee, which is responsible for authorization, is chaired by Senator Kennedy (D-MA) and has added three new members. Oversight is within the purview of the Homeland Security and Government Affairs Committee chaired by Senator Lieberman (I-CT).

Questions and Answers

Dr. Jean deKernion, Professor and Chairman, Department of Urology, David Geffen School of Medicine at UCLA, asked for clarification of the provision of the Reform Act relating to the organization of the NIH. Ms. Erickson noted that earlier drafts of reauthorization legislation had proposed changes to the overall NIH structure, but the reauthorization act requires only that a Scientific Management Review Board be established to consider whether there could be a better organizational structure for the NIH. Dr. Coffey asked where the decision was made to fold the NCI budget into a package for the NIH. Ms. Erickson explained that the Reform Act specifies a single appropriation for the NIH, but the House and Senate, as they write their appropriations bills, are free to include a line-item appropriation for each of the Institutes. Dr. Runowicz asked for information about the Brownback/Feinstein bill. Ms. Erickson

replied that it has not yet been introduced but appeared to be imminent, and she would keep the Board informed.

VI. AMERICAN ASSOCIATION FOR CANCER RESEARCH REPORT: ADVANCING THE PREVENTION AND CURE OF CANCER THROUGH RESEARCH, STRATEGIC LEADERSHIP, AND PARTNERSHIPS—DR. GEOFFREY M. WAHL

Dr. Geoffrey M. Wahl, Professor, Salk Institute, announced that he would be speaking today as President, American Association for Cancer Research (AACR), the largest and oldest cancer research organization in the United States, and as the son of parents who fought and lost the battle against cancer. He emphasized the importance of three messages he would deliver: 1) cancer research is working as evidenced by the first decline in cancer mortality in 70 years; 2) research efforts must be redoubled because of the increased incidence of cancer expected in the near future as the population ages and people are living longer; and 3) the view of scientists in the trenches is one of unbridled enthusiasm balanced by substantial concern that cancer research does not appear to be a priority. He began his formal report on the AACR by noting that the AACR and NCI share a common objective: to reduce the incidence and mortality due to cancer. The AACR and NCI have worked effectively to achieve common goals over many years through convening and co-sponsoring meetings on topics jointly identified. These efforts have focused on prevention, development of more effective therapeutics, methodology workshops to translate information from the bench to the clinic, imaging to provide more effective means of early detection, and training programs across all segments of society.

To substantiate his message that cancer research is working, Dr. Wahl cited data heard earlier from Dr. Niederhuber showing a progressive decline in age-adjusted death rates due to cancer and the first non-age-adjusted decrease in mortality: in 2003, 3,014 fewer people died of cancer than the prior year. He presented further data to illustrate the economic impact and return on investment of cancer research: a 1 percent decrease in cancer mortality was estimated by University of Chicago economists to be worth $500 B; estimated "savings" realized from the 3,014 fewer deaths in 2003-2004 is $279 B; advances in cancer treatment have applications for other diseases; the total cost of the "war on cancer" since 1971 is $69.3 B. The value of work through the cancer research area is tangible, he noted, not only in terms of economic savings, lives saved as well as the costs associated with those lives, applications for other diseases, and the spawning of new industries, but also in inestimable social returns on investment.

As evidence that a redoubled research effort is needed, Dr. Wahl reminded members that cancer is a disease of aging and by 2030, 20 percent of the U.S. population will be over the age of 65, compared with 12 percent in 2004. Cancer incidence in that age group is 10-fold greater and cancer mortality 16-fold greater. He characterized the looming cancer crisis as akin to a tsunami, but different in that the Nation has warning of the cancer crisis and its investment in research has prepared the research community to use the tools at hand to start solving the problem now. He stated that the public needs to be made clearly aware of the situation.

In regard to its core characteristics, Dr. Wahl reminded members that over the past 100 years the AACR has become the world's collective brain trust for cancer research. Its membership encompasses the many sub-fields of cancer research, from angiogenesis to virology, to address problems related to cancer prevention, detection, and cure. Moreover, the AACR's diverse scientific scope creates a unique environment for crossdisciplinary interactions and research integration. Dr. Wahl presented examples of the means by which the AACR drives the scientific agenda on several fronts to hasten progress. 1) To identify and promote new and promising research opportunities, interventions, and strategies, a Council of Scientific Advisors was established with the charge to review the status of cancer research, identify promising areas, elucidate bottlenecks, and propose solutions and milestones for achieving them. 2) To

foster creativity and innovation in cancer research, people from different fields are brought together to think in different ways than they normally would to create opportunities that are synergistic instead of just additive. The various mechanisms used include annual meetings, scientific think tanks, educational workshops, and task forces. One example of this is the AACR Epigenome Project, which had its beginnings in a workshop that identified problems in epigenetics as important to cancer etiology. A task force was formed to identify the technologies needed and an idea of how to pursue such a project. That has led to the generation of a proposal that has been submitted to the NCI to implement the project.

The AACR works in three areas that can lead to decreases in cancer incidence and mortality: **prevention, early detection, and treatment**. Although significant progress has been made in **cancer prevention** because of advances in basic, translational, and clinical research, challenges remain and a transdisciplinary approach is needed to address the many etiologies of cancer and many appropriate ways in which prevention can be implemented. To be more successful at prevention efforts from a scientific perspective, biological targets, evidence-based approaches, biomarkers of success, and milestones to monitor the cancer prevention strategy in real time are needed. The AACR stimulates this work in these areas by working closely with the NCI and Food and Drug Administration (FDA) and through meetings such as the AACR International Conference on Frontiers in Cancer Prevention Research; publishing a journal—*Cancer Epidemiology, Biomarkers & Prevention*; establishing a Cancer Prevention Task Force for developing a comprehensive strategy based on basic research principles; and exploring new avenues to increase the dissemination of leading prevention science research. The importance of public education as a key element for prevention was underscored by the percentages of people in the United States and Great Britain, particularly those in the highest risk groups, who believe they can do nothing to alter cancer risk. The AACR, as well as the NCI and ACS, is working to make information about cancer more accessible.

In the area of **early detection**, Dr. Wahl noted that the AACR meeting convened in September 2006, on Molecular Diagnostics in Cancer Therapeutic Development was so successful that plans are underway to hold another this year in recognition of the speed with which the field is moving. The AACR worked with the NCI and FDA to generate the joint Think Tank of Clinical Biomarkers held last year in Philadelphia recognizing that clinical biomarkers will be an important metric in the future for prevention research and for determining the effectiveness of personalized therapeutics. In addition, the AACR dedicates sessions on detection and diagnostics in its Annual Meetings and has convened a Workshop on Early Detection Research to bring together the various facets of early detection research to enable the development of new approaches in this area.

In the **cancer treatment** area, AACR initiatives to accelerate progress in translational research and cancer medicine include international collaborations such as the International Conference on Molecular Targets and Cancer Therapeutics in partnership with the NCI and the European Organization for the Research and Treatment of Cancer (EORTC) and a conference entitled "In the Forefront of Basic and Translational Cancer Research" in partnership with the Japanese Cancer Association, which has been held annually for the past 7 years. Other initiatives are the Translational Breast Cancer Research Grant Program; think tanks on translational medicine, including one to be held in July; and an International Meeting Series on Translational Cancer Medicine. The AACR emphasized the importance of people working together to translate discoveries from the bench to the patient by offering the Landon Prize for Translational Cancer Research, as well as the Rosenthal Award in recognition of pioneers in this area. Dr. Wahl noted that incoming president, Dr. William Hait, well-known in the field of translational research and a member of the BSA, will continue to pursue the AACR vision of growing a new generation of translational cancer researchers. The objective is to develop a new infrastructure to ensure a firm grounding in basic research that will enable them to translate those findings into the new drugs of the future.

Dr. Wahl noted that, in driving the scientific agenda, the AACR understands the need for engaging in synergistic partnerships both nationally and internationally, inasmuch as cancer is a set of diseases that know no geopolitical boundaries, and cancer mortality rates are greater outside the United States. To work on reducing these disparities, the AACR is forming partnerships worldwide to transfer technology from the United States to other countries, gain access to new drug and treatment approaches, and work collaboratively to even out the effectiveness of cancer prevention, detection, and treatment. The AACR also is committed to eliminating cancer health disparities in the United States. The AACR Minorities in Cancer Research (MICR) Council meets regularly to provide advice on areas of emphasis needed to reduce disparities, and a special session on this topic will be featured in the 2007 Annual Meeting. In recognition of their work to reduce health disparities in certain U.S. populations, the AACR's 2007 Public Service Award will be given jointly to Dr. Leffall and Dr. Harold Freeman. Later in the year, the AACR and the NCI are co-sponsoring the Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved.

Dr. Wahl commented briefly on the AACR Annual Meeting to be held April 14-18 in Los Angeles, CA, in this centennial of the AACR's founding in 1907. He outlined several new and important features for this meeting: educational organ site sessions at the clinical-basic-science interface and three sessions on drug development in the various stages to emphasize the AACR's translational research efforts, from concept and Phase I trials to Phase II proof-of-concept trials to Phase III clinical trials. Dr. Wahl noted that the AACR centennial provides an ideal opportunity to draw public attention to the importance of cancer research; therefore, a number of centennial events and initiatives are planned. The AACR also will, as one even associated with its Centennial, hold a Lobby Day in Washington, DC, in May 2007, and honor several members of Congress who have been ardent supports of cancer research.

Next, Dr. Wahl conveyed the view from the trenches—what AACR members are saying. He noted that these scientists view the unparalleled opportunity with optimism and enthusiasm: technology is more powerful than ever before and the knowledge base is greater. They have serious concerns, however, for the future of cancer research that are related to inconsistent and insufficient funding. Dr. Wahl cited evidence that the United States is losing the next generation of researchers, and he presented his concept of what is happening. Over the past 35 years of the National Cancer Program, a well-running machine has been built that addresses all areas critical to diminishing the incidence of and mortality due to cancer. It runs on the basis of investigator-initiated awards, team science, and grants that support big science, and all parts must work in concert for the machine to work effectively. With the kind of budget decreases being seen, basic research is in danger and its loss would have an impact on translational and clinical research. Dr. Wahl noted that the AACR is looking at a variety of ways to mitigate the problem. During his tenure, the AACR Centennial Grant Research Fund was initiated, which emphasizes leverage funding: money obtained from the private sector and philanthropies is combined with AACR funds to help fund new investigators, new and innovative research, and areas of great opportunity. In addition, the message that the cancer rate is down but the war is not won is being disseminated consistently and firmly through the media and through the science policy and legislative affairs activities of the AACR. The goal is to make cancer research a national priority again and underscore the urgency of the need to move forward quickly.

Dr. Wahl concluded by reiterating that the AACR and NCI have shared missions and goals. He proposed working more closely to identify, in an objective way, what research priorities the community considers critical, where opportunities exist, how resource utilization can be optimized in times of fiscal challenge, and how translational research can be strengthened. In this way, it will be possible to achieve the goal of optimizing research opportunities today to ensure a competitive and productive cancer research enterprise for tomorrow in which all patients will benefit.

Questions and Answers

Dr. Moon S. Chen, Associate Director, Cancer Disparities and Research, University of California, asked for further information on the AACR Comprehensive Minority Biomedical Branch Program for minorities and the medically underserved. Dr. Margaret Foti, CEO, AACR, explained that travel grants for minority investigators have been awarded for attendance at annual meetings through the program for many years. In addition, deliberations in a think tank, co-funded by the NCI, formed the basis for the upcoming AACR conference on the science of cancer health disparities. Ms. Giusti commended the AACR's move into grant support, and she asked about the annual budget and how the fields to be funded would be chosen. Dr. Wahl pointed out that the program is in its first year, so the budget is modest. In regard to the fields to be supported, areas of opportunity and novel mechanisms are being identified and proposed to the Board for approval. One initial emphasis will be to support outstanding young investigators, but several fields will be considered. In an attempt to leverage the available resources, Centennial Grant Partners are being sought to donate a certain amount of money that will be matched with the money raised by the AACR to fund either a field or a new investigator. Other strategies are being tried to raise more money in the future as people see the success of the early program.

VII. BREAST CANCER STAMP INITIATIVE—DRS. DINAH SINGER AND BARBARA V. VONDERHAAR

Dr. Dinah Singer, Director, Division of Cancer Biology (DCB), described the NCI Breast Pre-Malignancy Program as a novel trans-NCI initiative in which all Divisions are pursuing various aspects of breast pre-malignancy. Members were reminded of the background of the current program. In 1997, Congress recognized the need to increase public awareness about the breast cancer problem and raise funds to support research. To address this need, the Stamp-Out Breast Cancer Stamp Act was enacted, which authorized the U.S. Postal Service to issue a special stamp with a surcharge of $.08 above the first-class postage rate. The donated funds were allocated to the NCI (70%) and Department of Defense (DoD) Breast Cancer Research Program (30%). The Act was reauthorized through 2007. As of FY 2006, the NCI has received a total of $35.2 M, which has been used in support of two programs: Insight Awards to Stamp-Out Breast Cancer, which fund R21 grants in high-risk research, and Breast Cancer Research Stamp Act Awards, which funds R01 proposals focused exclusively on breast cancer that fall just outside the payline. For FY 2007, the NCI has $8.3 M from the fund to support additional breast cancer research, and breast pre-malignancy research was identified as the target area for use of the funds. The Program was established, and a Trans-NCI Steering Committee was formed to oversee and integrate the Program.

Six research components selected by the NCI EC for support were: 1) biology of breast pre-malignancy (DCB); a Request for Applications (RFA) will be issued shortly; 2) molecular epidemiology and mammographic density (Division of Cancer Epidemiology and Genetics [DCEG]); 3) evaluation of decision-making approaches used by women recruited to chemoprevention trials for breast cancer (Division of Cancer Prevention [DCP]); 4) evaluation strategies to improve accuracy of mammography interpretation with the Breast Cancer Surveillance Consortium research resources; co-funded by ACS (Division of Cancer Control and Population Sciences [DCCPS]); 5) MRI-guided therapy with targeted SPIO carbon nanostructure; supplement to a breast cancer Specialized Programs of Research Excellence (SPORE, Division of Cancer Treatment and Diagnosis [DCTD]); and 6) isolation, propagation, characterization, and imaging of breast cancer stem cells to improve early diagnosis and therapy of breast cancer; and development and characterization of antibody-based bioconjugates for molecular imaging and targeted therapy of HER 2-positive breast cancers (CCR]). Dr. Singer introduced Dr. Barbara K.

Vonderhaar, Co-Chair, Breast and Gynecologic Malignancies Faculty, CCR, to describe the large intramural effort to characterize and image breast cancer stem cells.

CCR Breast Cancer Stamp Fund Program. Dr. Vonderhaar explained that the two projects that comprise the CCR program are based on the concept of the stem cell in the breast. She noted that, although the presence of a stem cell or stem-like cell in the breast has been known in animal models for many years, little research has been focused on humans. Members were reminded of the functional definition of stem cells: they are self-renewing, able to replicate, and give rise to multipotent progenitors, which ultimately give rise to the differentiated cell lineages within the breast. The concept is similar for the cancer stem cell in the breast: cancer arises either from the normal stem cell or from the pleuripotent progenitor cells, which give rise to a cell within the solid tumor that has the characteristics of a stem-like cell. The cancer stem cell also is self-renewing and gives rise to the more differentiated or bulk of cells within the tumor. Dr. Vonderhaar cited research at the University of Michigan, which concluded that the expression of high levels of CD44 and low or absent levels of CD24 in surface markers on breast cancer cells defined a subpopulation of breast cancer cells that had stem-like characteristics and gave rise to tumors when injected at very low levels; the resulting tumors contained all of the cell types. She noted that this finding is important in terms of therapy in that current therapies are directed towards killing the majority of cells within a tumor, but if the stem cells survive the tumor can recur. The hypothesis is that the tumor eventually should degenerate if drugs are designed that kill the stem cells whether or not the majority of cancer cells are attacked in the process. This premise forms the basis for the CCR two-part program.

Project 1: Isolation, Propagation, Characterization, and Imaging of Breast Cancer Stem Cells to Improve Early Diagnosis and Therapy of Breast Cancer is based on the hypothesis that breast cancer stem cells can be characterized by unique cell surface markers that can be used for targeting molecular imaging probes and directing molecular therapy. Project 2: Development and Characterization of Affibody-Based Bioconjugates for Molecular Imaging and Targeted Therapy of HER2-positive Breast Cancers is based on the hypothesis that delivery of therapeutic substances to HER2-positive breast cancers can be optimized using conjugates of HER2-specific affibody molecules with multifunctional thermosensitive liposomes.

Specific aims of Project 1 are to: 1) identify and localize the stem and progenitor cells in human breast from normal and high-risk women, as well as those from malignant neoplasms; 2) define a functional assay for the normal stem cell and its niche in humanized mouse mammary fat pads; 3) develop targeted imaging methods; and 4) develop improved chemotherapy for breast cancer by targeting the breast cancer stem cell niche. Milestones have been established for monitoring progress during the 3-year project period, and a multi-disciplinary, multi-Institute, and multi-institutional team of principal investigators has been assembled to carry out the project. Immediate goals for the first year are to: 1) catalog existing samples from various protocols, amend existing protocols, and write new protocols to expand the tissue collection; and 2) standardize processing of samples; 3) optimize growth conditions *in vitro* for human breast stem cells; 4) optimize the *in vivo* growth conditions for normal breast epithelial cells; and 5) validate the practicality of doing microarray and proteomic-type analyses on very small populations of cells. Tissues are being obtained from Suburban Hospital, the NIH Clinical Center, Bethesda Naval Hospital, and Walter Reed Army Hospital, and a colony of NOD/SCID mice has been developed in the NIH specifically for this CCR program. Dr. Vonderhaar noted that patient information is being collected with the tissue samples so that questions can be researched later about family history, hormone replacement therapy, and other parameters involved in breast cancer risk. The data are de-identified so that patients cannot be identified.

Next, Dr. Vonderhaar reminded members that stem cells currently are defined by function. She discussed research in her laboratory aimed at defining both cancer and normal stem cells at a molecular

level. Because the function of the normal and cancer stem cell is to give rise in the normal gland to all other types of cells, the challenge in her work has been to maintain and expand the stem cell population when it is in culture and minimize the differentiation and production of daughter cells. Of the variety of pathways or growth factors and hormones being studied to accomplish this, the CCR scientists have had some success with the hormones, particularly prolactin and estrogen, and are now looking for synergy between the two. Dr. Vonderhaar gave a detailed description of work to develop a functional assay for a normal mammary gland and ascertain whether a stem cell has been identified. The work builds on a finding by Dr. Charlotte Kuperwasser, now on the CCR project's external advisory committee, who was able to humanize the mouse mammary fat pad by introducing human mammary fibroblasts, allowing 4 weeks for them to humanize, and adding epithelial cells together with other fibroblasts; an actual mammary gland was isolated after a growing period of 8-12 weeks. This work has been recapitulated by CCR scientists with their cells; plans include adding epithelial cells from both normal and at-risk women as well as different types of fibroblasts, both normal and those from tumors and women at high risk for breast cancer—the latter because of the importance of the epithelial mesenchymal interactions in the development of the breast.

Dr. Vonderhaar noted that the normal human breast has two types of stroma—intralobular and interlobular—which are quite distinct. She described work in which laser capture microdissection was used to obtain either intra- or interlobular stroma, RNA extracted, and microarrays performed. The data have been received and are being analyzed to identify surface markers that will distinguish these two fibroblast types. It has been possible to grow all kinds of fibroblasts on plastic, including tumor fibroblasts from spontaneous tumors from BRCA-1 patients and normal fibroblasts from the general population and BRCA patients. The question to be answered is whether the fibroblasts growing on plastic express the surface markers that distinguish the two normal populations. Dr. Vonderhaar described additional research based on the idea that mammospheres, which constitute one way to grow normal epithelial cells, may be a surrogate for identifying stem-like cells from the normal gland. While waiting for the conditions for isolating normal epithelial cells from fresh tissue to be standardized, the decision was made to try to optimize conditions using two cell lines (normal gland and highly aggressive tumor line) from a staged series of human breast-derived cell lines representing different steps in cancer progression developed by Dr. Fred Miller, Karmanos Cancer Institute. The normal cell line was found to grow beautiful mammospheres, and these have been implanted in the humanized fat pads of the mouse model.

Finally, Dr. Vonderhaar described research on a functional assay for tumors using pleural effusions in the mouse model. She reiterated the finding by the Michigan group that a stem subgroup of cells could be defined as CD44+/CD24- or low. She described a series of CCR studies, including one in which the cells from two breast cancer pleural effusion samples were presorted into CD44+/CD24+ or CD44+/CD24low before implanting in the mouse model, and the resulting tumors were analyzed molecularly. The conclusions reached were: 1) CD44+ appears to be a marker for tumor formation *in vivo*; 2) CD24low/- does not appear to correlate with tumor formation *in vivo*; and 3) new, additional markers are needed to better define the tumor stem cell on the molecular level. Dr. Vonderhaar explained that this search for new markers is being conducted by selecting for tumorspheres from the pleural effusions; doing microarrays on them to find unidentified molecules, and then, using the aggressive MCF10A IV cell line because the number of cells from the pleural effusions is limited, looking at a variety of known markers that have been implicated in embryonic stem cells and other types of cancer as possible markers. The goal is to identify a better molecular signature for the stem-ness of the cancer-initiating cells as well as the normal mammary gland so that the signature can be used to improve imaging and the targeting of therapy.

Questions and Answers

Dr. Coffey commended the work that had been presented. He asked whether there are any plans to exchange cells with the Michigan group to resolve the different conclusions related to CD24- and whether Matrigel was being used to enhance the take of the tumors. Dr. Vonderhaar replied in the affirmative to both questions. Dr. Coffey wondered whether angiogenesis might be the problem. Dr. Vonderhaar replied that it had not yet been ruled out. Dr. Judah Folkman, Director, Vascular Biology Program, Children's Hospital of Boston, also commended the work, and he described findings from studies in his laboratory looking at breast cancer that relate to the CCR project. Dr. Wahl commented from the AACR perspective that cancer stem cells have been identified as important to study and problems in the field are understood. An AACR workshop was convened in 2006, which produced a position paper outlining the problems related to defining the stem cell and addressing issues related to standardization of technology and reagents. The decision has been made to establish a work force to further the field. He suggested that this is an area where the NCI and AACR could collaborate. Dr. Vonderhaar reemphasized the importance of standardized conditions under which epithelial cells are obtained so that comparisons can be made across laboratories, not only for the cancer stem cell but also in normal tissue. She noted that the CCR group is working on a solution that they hope to be able to provide both intra- and extramurally for scientists in the entire field.

VIII. CHALLENGES AND OPPORTUNITIES FOR FACING NIH PEER REVIEW: A VISION FOR ENSURING ITS STRATEGIC NATIONAL VALUE—DR. TONI SCARPA

Dr. Toni Scarpa, Director, Center for Scientific Review (CSR), NIH, described activities in streamlining the NIH grant application process. Of approximately 80,000 applications submitted to the NIH each year, 55,000 are reviewed by 18,000 CSR reviewers. In addition, there are 250 Scientific Review Administrators and 1,800 review meetings annually held by approximately 600 study sections. In 2006, the NCI R01 study sections scored 13 percent of applications at 10 percent, compared to the NIH baseline of 10 percent of applications receiving that score; in peer review, the study sections are 30 percent above the NIH average.

Peer review is at the heart of the NIH and has created the best academic medical centers, biomedical/behavioral research, and biotechnology. It has made possible the best cures and prevention, been admired and imitated within and outside the United States, and has protected the NIH against outside influence. There have been, however, several complaints made about the NIH peer review system, including: the slowness of the process; the dearth of senior/experienced reviewers; the bias toward predictable research instead of significant, innovative, or transformative research; the bias against clinical research; and the burden posed by the amount of time and effort involved in the process, including resubmissions. Dr. Scarpa noted that, over the years, the diseases of America have become more chronic than acute and will affect every organ and tissue, and that research is being conducted with the use of large, collaborative groups. The NIH system, with its system of face-to-face peer review meetings, cannot cope with the current workload.

Dr. Scarpa described a preliminary vision for a peer review system. One is to maintain the current *status quo*. Several changes are underway to refine CSR operations, such as increases in communication, transparency, and uniformity. Additionally, improvements in efficiency have involved the retooling of the R01 application for electronic submission through the use of text fingerprinting and artificial intelligence software; this eventually will be followed by electronic review. Currently, there are 145 to 150 steps of verification; the electronic review system will save about 1 month of time in the review process and require about 20 to 25 fewer scientists.

Changes made to the peer review process will affect all NIH Institutes and investigators, and so all stakeholders need to work together. These changes include: shortening the review cycle; improving the study section alignment and performance; addressing the concern that clinical research is not properly evaluated; recruiting and retaining more high-quality reviewers and decreasing the burden on applicants and reviewers; and improving the identification of significant, innovative, and high-impact research. The goal is to provide every applicant with a score and a summary statement within 3 months of application submission so that they have 1 month to decide to reapply, and up to three reviews could be conducted within 1 year rather than taking 3 years. Every summary statement now is posted 1 month after the study section, and every *R01 investigator receives a summary statement within 1 week of the study section. In a pilot short review cycle of *R01 applications involving 40 study sections, 13 percent of the eligible investigators reapplied and most resubmitted applications are two times better than the average. In March, this will be increased to 62 study sections, and in June to 100; by November, all investigators will have the possibility to decide to resubmit their applications within 4 months. To improve study section performance and better align the science of some disciplines, the 14 Integrated Review Groups that existed in 2006 were streamlined into 9 groups for 2007. Additionally, to receive input from the scientific communities, six open-house workshops will be held in 2007. Dr. Scarpa also said that the quality of clinical science reviews has been a concern; a significant number of clinical grantees do not submit renewal applications. The recruitment of reviewers remains a challenge. Applications to the NIH have risen significantly during the past 5 years, from 46,000 to 80,000. Although the number of non-chartered reviewers has nearly doubled in that time, the number of chartered reviewers (i.e., the permanent mentor study section) has risen significantly less. Short-term solutions to address these issues include: reducing travel requirements by using electronic review modes, holding shorter meetings, and using shorter applications. There is strong support for a shorter application from most stakeholders, including the councils of professional societies. This will allow each reviewer to read more applications, smaller study sections, and the recruitment of more experienced reviewers. Furthermore, reviews can be more focused on impact and innovation and less on approach and preliminary results.

A third consideration is whether a completely different system should be adopted. Dr. Scarpa will be discussing this possibility with his colleagues in the future. Dr. Scarpa closed with the idea that the true mission or value of peer review is in the millions of lives that are saved every year because peer review identified the best research, treatment, and prevention for their disease. He invited NCAB members to contact him directly if they have a need.

Questions and Answers

Dr. Runowicz asked if the reduced number of clinical research applications was a result of investigators not applying or investigators asking a focused question rather than a series of research questions such as a basic scientist would submit. Dr. Scarpa believed it was a combination of both, but data are not available to confirm this. Dr. Niederhuber recalled data that showed that clinician scientists decide not to reapply because of the extensive frustrations encountered throughout the process. Dr. deKernion said that the barriers or obstacles to reapplications likely vary. Dr. Lloyd Everson, Vice Chairman and Member of the Board of Directors, US Oncology Incorporated, agreed that frustration with the application review process constitutes a major reason that young people leave academic medicine.

Dr. deKernion commented that, although there are problems with videoconferencing, people likely would be more willing to participate if they did not have to travel. Dr. Scarpa said that the electronic mechanism works well. Ms. Giusti expressed support for the move to the electronic format. Dr. Chabner said that, with the electronic review, the essential discussion on the fundamental issues about whether a specific line of research is worth pursuing would be lost.

Dr. Coffey said that the SPOREs Program has supported young investigators who became successful when other mechanisms failed. He also noted that different players in the field, even within the NIH organization, often contradict each other on the state or plight of new investigators. Dr. Folkman echoed the importance of the participation of senior scientists in study sections; such people are experienced enough to know that sometimes a young investigator has a bright idea that is not expressed as clearly as one might like. He suggested that more flexibility in the NIH study section guidelines, such as allowing the study section to call an investigator during its meeting, might help the reviewers. Dr. Scarpa responded that transparency and consistency in the treatment of all applicants must be maintained during the review. He further added that new investigator applications fare about the same as a new application from an established investigator but not as well as recompeting applications from established investigators. There also are study sections that review only new investigators' applications. Dr. Chabner commented that capable young M.D. and Ph.D. researchers exist, but study section reviewers try to create the perfect experiment rather than ask the question of whether this is a promising young person whose career should be supported.

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

Dr. Gray reviewed and requested concurrence by the NCAB in two Delegations of Authority to the Director, NCI, so that he can function in his capacity as 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 for 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:** 1) grants with direct costs that are $50,000 or less, as well as Individual National Research Service Awards; 2) applications over the 50th percentile will not have summary statements presented to the NCAB; and 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; and 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.

X. NCI BIENNIAL REPORT: INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH—DRS. PAULETTE S. GRAY AND MICHAELE CHRISTIAN

Dr. Gray said that the *Biennial Review of Inclusion of Women and Minorities in Clinical Research* report will be signed by the NCI Director and submitted to the NIH, which will include this information in the NIH's report to Congress that describes the work of all the ICs. She recognized DEA and other NCI staff who assisted in compiling the data for the report and introduced Dr. Michaele Christian, Associate Director, Cancer Therapy Evaluation Program (CTEP), DCTD.

Dr. Christian reported on the NCI's accrual data in response to the NIH policy on the inclusion of women and minorities in clinical research. The policy was mandated by Congress in 1993 and is based on the ethical principle of justice and the importance of balancing research burdens and benefits. Public Law (PL) 103-43 states that women and minorities must be included in all clinical research studies, including Phase III clinical trials. Trials must be designed to permit a valid analysis—that is, an unbiased assessment that does not require high statistical power and is to be conducted for both large and small studies. Cost is not allowed as an acceptable reason for exclusion, and the NIH supports outreach efforts to recruit and retain women, minorities, and their subpopulations in clinical studies. The NIH Revitalization Act of 1993 mandates that "The Advisory Council of each National Institute shall prepare biennial reports describing the manner in which the Institute has complied with this section." The reports are completed for odd-numbered years. The NIH report approach involves a summary report prepared centrally by the NIH Office of Research on Women's Health and includes a statement that the NCAB reviews. The statement covers NCI procedures for the implementation of the NIH policy, the results of that implementation, and NCI compliance.

NCI's DEA coordinates this activity and implements the inclusion policy. It is responsible for NCI-wide coordination and communication. In addition, an Accrual Working Group includes representatives from NCI Divisions and is responsible for information, training, and problem-solving in this area. Health science administrators (HSAs) work with applicants to disseminate these requirements using the NIH Guide and Web sites. Extramural staff are kept informed through a trans-NIH educational program and the desktop distribution of policies and procedures. Pre-award activities include the following: peer reviewers receive instructions on policies and evaluate inclusion plans; when concerns are noted, bars to awards are put into effect, and NCI staff work with applicants to ensure that appropriate revisions are made; and applications with bars are identified in closed NCAB sessions and any subsequent resolution is reported. For post-award monitoring, awardees are responsible for reporting cumulative accrual annually. The progress of studies and cumulative accruals are reviewed by Program Directors. Moreover, target and enrollment numbers are entered into the NIH Population Tracking application, and staff work with awardees to disseminate findings and encourage new studies. Aggregate reporting is used, as the NIH requires a format that aggregates all Phase III clinical trials, whether based on treatment, behavioral, or epidemiologic observation. The data for individual clinical trials vary considerably, and large, population-based screening and observational trials dominate aggregate data.

Dr. Christian next described overall reporting data, followed by data specifically for cancer treatment trials. An OMB directive in 1997 created racial and ethnic standards for Federal statistics and administrative reporting that was required to be implemented by 2003. Changes were made in requirements for population types to correspond to the 2000 census data collection. "Hispanic," for example, became an ethnic category, and data had to be collected in this category, in addition to race and gender. Instructions in the Public Health Service Grant Application (PHS 398) dictate that the inclusion

of women and minorities must include subject selection criteria and rationale; the rationale for any exclusion; enrollment dates (i.e., start and end dates); outreach plans for recruitment; and the proposed composition of the study using new tables. For accrual to NCI clinical trials, data must include epidemiological, population-based interventions and therapeutic trials. Subset analyses by race, ethnicity, and gender are required for all Phase III clinical trials with funding after 1995. The current cycle of reporting covers FY 2005 and 2006, which represent subjects enrolled during FY 2004 and 2005. A Phase III clinical trial is defined as a broadly based prospective Phase III clinical investigation that usually involves several hundred or more human subjects to evaluate an experimental intervention or compare two or more existing treatments. Often the aim of such an investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care.

Dr. Christian concluded with data from the U.S. 2000 Census and Phase III enrollment research studies reported in the older and newer reporting formats, including the change in reporting ethnicities; the data illustrated the complexity of racial composition, cancer incidence rates, and enrollment data for extramural and intramural research studies, ethnic categories, and sex/gender.

This was followed by details of enrollment data for CTEP Treatment Trials for FY 2005 and 2006, including by gender, race, and ethnicity. During a 10-year period (1995-2006) about 83 percent of CTEP accrual was White patients, about 8 percent Black, 5 percent unknown, 2 percent Asian, and about 0.4 percent American Indian. In that same timeframe, accrual by gender totaled about 60 percent women and about 38.5 percent men, with 2 percent unknown (i.e., not supplied). If gender-specific trials are excluded, the gender distribution changes to about 41 percent female and 59 percent male. In FY 2005, the accrual rate was about 5 percent Hispanic, 81 percent non-Hispanic or non-Latino, and 13 percent unknown. The racial distribution was 85 percent White, 8 percent Black, 3 percent unknown, 2.5 percent Asian, and 0.5 percent American Indian or Alaska Native. The accrual numbers remained relatively the same in FY 2006, except that Black patients totaled 7.3 percent and the unknown rate increased some. By gender, accrual rates in FY 2005 were 55 percent female and 37 percent male; for FY 2006, they shifted slightly to 62 percent female and 38 percent male. For both years, the numbers are approximately the same when gender-specific trials are excluded: 41 percent females and 59 percent males.

Questions and Answers

Dr. Chen queried about the breadth of the studies covered. Dr. Christian said that the report encompasses domestic and international studies; she noted the difficulties of excluding specific populations, such as Asians, to better reflect the proportion of the U.S. population.

Dr. deKernion asked whether a potential or new enrollee in a clinical trial is legally required to state race or ethnicity. Dr. Christian expressed doubt about such a legal requirement but pointed out that, consistent with the new race and ethnicity data reporting, a much higher "unknown" fraction is now being reported than in the past. Dr. Gray said that individuals who are submitting grant applications and conducting clinical research must indicate the accrual numbers based on race and ethnicity; there is no way of knowing, however, how they ascertain the numbers that they report. Dr. Chabner commented that it likely is based on subject self-identification, and he described difficulties in determining whether the Portuguese-speaking population from Brazil, for instance, should be considered Hispanic or not. A similar confusion exists for people from the Dominican Republic who are Spanish speaking but African in heritage.

Dr. deKernion said that, although the report is informative, it does not address major issues about accrual rates that are of interest to NCAB members. Dr. Gray clarified that the NIH was mandated to report on specific information in the report, and that many of the report's data are not specific to any of

the disease areas that are germane to cancer. Dr. Chabner asked whether the data could be aggregated differently for the NCAB to make it more useful to increase accrual for the cancer treatment trials. Dr. Kenneth Cowan, Director, UNMC Eppley Cancer Center, Eppley Institute for Research in Cancer, University Nebraska Medical Center, and Dr. Folkman agreed that it is important to use the data to help change accrual barriers. Dr. Christian said that data could be presented to help the NCAB with this; she noted that to meet a Congressional requirement, however, the data also need to be presented to the NCAB in the context of the NIH's report.

In response to a question from Dr. Runowicz, Dr. Christian said that more women are accrued to clinical research studies than men, even excluding gender-specific studies except for the cancer treatment trials.

Motion. A motion was made to approve the *Biennial Review of Inclusion of Women and Minorities in Clinical Research* as presented. The motion was seconded and approved unanimously.

XI. ANNUAL REPORT: IMPLEMENTATION OF CLINICAL TRIALS WORKING GROUP RECOMMENDATIONS—DR. JAMES DOROSHOW

Dr. James Doroshow, Director, DCTD, provided an update on the implementation of the Clinical Trials Working Group (CTWG) recommendations to enhance the integrated management for the clinical trial system issues related to prioritization, coordination, standardization, and operational efficiency.

To improve **enterprise-wide integrated management**, the CTWG recommended the establishment of an external clinical trials oversight committee to advise the NCI Director, as well as the development of a coordinated, organizational structure within the NCI to manage the clinical trials enterprise. In response, the CTAC and Clinical Trials Operations Committee (CTOC) were formed. The CTAC was chartered as a Federal advisory committee in March 2006, and held its first meeting in January 2007. Its membership consists of 10 members of other current NCI advisory boards and 14 additional members from the extramural clinical trials community. The CTAC provides extramural oversight for CTWG initiatives and strategic advice regarding the entire NCI clinical trials portfolio, advises on the use of correlative science and quality of life (QOL) funds, recommends refinements to the NCI-supported clinical trials system, and advises on the outcome of formal evaluations. The CTAC currently includes three working groups focused on informatics, public-private partnerships, and coordination issues. Its next meeting is scheduled for June 2007. The CTOC was established in December 2005, and includes membership from all NCI Divisions, Offices, and Centers involved in NCI-supported clinical trials. To date, the CTOC has reviewed all RFAs and Program Announcements (PAs) involving clinical trials during the past year, provided input to the NCI Center for Bioinformatics (NCICB) on the CTWG informatics implementation plan, worked on evaluating the feasibility of modifying clinical data reporting requirements for grant-funded trials, and approved minority accrual supplements. Its portfolio reviews encompass programmatic and disease-specific areas. The Coordinating Center for Clinical Trials (CCCT) ensures integrated management between the CTOC, CTAC, the NCI Director, Divisions, Centers, and Offices, and the extramural clinical trials community.

Prioritization and scientific quality involves all stakeholders in the design and prioritization of clinical trials that address the most important questions using the tools of modern cancer biology. An Investigational Drug Steering Committee with five task forces has been established. For the first time, extramural input was received in the development of a drug development plan before it was disseminated nationally to the Phase I investigator community. Active scientific steering committees cover gastrointestinal, gynecologic, and head and neck cancers. An additional Scientific Steering Committee on Symptom Management and Health-Related QOL will hold its first in-person meeting in May 2007; it will

involve NCI's DCTD, DCCPS, and DCP to help advance the sciences of symptom management and begin a national prioritization process. The steering committees include SPORE members, community oncologists, and advocates. An important activity underway by one of the task forces is the development of a set of criteria to determine how to judge and prioritize correlative science in the context of Phase III clinical trials. Dr. Doroshow outlined several 2007 goals for this area: 1) the expansion of the role of the Investigational Drug Steering Committee for early phase trial prioritization, with new task forces helping to develop standards for biomarkers and review clinical development plans for angiogenesis and signal transduction inhibitors; 2) the implementation of the head and neck and symptom management/QOL steering committees; and 3) the development of standard protocols and standard laboratory practices for studies in the context of Phase III trials, as well as a biomarker standardization workshop.

Coordination initiatives will establish a comprehensive database containing regularly updated information on all NCI-funded clinical trials and to realign NCI funding, academic recognition, and other incentives to promote collaborative team science and clinical trial cooperation. Such promotion would be helped with modifications to award guidelines and funding practices. In addition, new forms of recognition could be created for cancer clinical investigators.

There are four **standardization** initiatives underway. 1) One is to create an informatics infrastructure that is interoperable with the cancer Biomedical Informatics Grid (caBIG™). A caBIG™ Clinical Trials Steering Committee—consisting of clinical trialists, statisticians, and information technology (IT) experts—was formed and will hold its first meeting in March 2007. 2) An inventory of NCI electronic Case Report Forms (CRFs) is underway to advance the development of standard CRFs that incorporate common data elements. 3) A credentialing system for investigators and sites will be developed that is recognized and accepted by the NCI, industry sponsors, clinical investigators, and clinical trial sites. 4) To begin promoting the establishment of commonly accepted clauses for clinical trial contracts, a preliminary meeting has been held with industry on the topic.

Operational efficiency is important in a time of a declining budget. Initiatives addressing this involve an ongoing financial analysis of NCI's Phase III funding model, particularly looking at institutional barriers that prolong the time from concept approval to the accrual of the first patient and improved outreach to enhance patient accrual. To illustrate the need for greater efficiency in operations, Dr. Doroshow showed a process flow map for Phase III studies that reflects the 384 steps currently needed to develop a trial in the Cancer and Leukemia Group B (CALGB). To enhance minority accrual, a trans-NCI partnership has been formed to look at mechanisms to solicit concepts, and the FY 2007 budget calls for expansion of this activity. Other issues being addressed are the barriers to the acceptance of the NCI's Central Institutional Review Board (CIRB) and the potential cost savings that would result from its use.

Dr. Doroshow concluded with a brief discussion of evaluation and outcome measures. A structured evaluation system has been designed by experienced evaluation specialists to include a blend of quantitative and qualitative measures; it has been reviewed by an external clinical trials expert panel. The NCI has initiated the first baseline evaluation for all of the issues related to implementation activities for the CTWG with respect to FY 2005 Phase I, II, and III trials with center directors, cooperative group directors, SPORE PIs, and members of the internal and external communities. The data will serve as the baseline against which to measure the impact of the implementation activities from the CTWG. This information will be reported to the NCAB when it has been compiled.

Questions and Answers

Ms. Giusti asked whether contracting and accrual rates would be measured, and whether the data would be extrapolated by cancer center. Dr. Doroshow said that the metrics have been established. Approval from the Cancer Centers would be needed to segregate the data by Center, as the data compilation and analysis is being conducted in a positive and nonpejorative fashion.

Dr. Chabner asked whether scientific review is required for an NCI-approved protocol. Dr. Ernest T. Hawk, Director, Office of Centers, Training and Resources (OCTR), responded that guidelines are being interpreted through the prioritization process within individual centers; the CTWG implementation process is trying to make the review criteria consistent across all platforms. An NCI staff member further explained that the current policy is that the protocols should be examined for prioritization compared to institutional protocols, but that the committee does not need to review for scientific merit or quality. Dr. Runowicz suggested that the committees who perform the Cancer Center reviews should have this formalized for them before they conduct onsite visits.

Dr. Cowan expressed appreciation for the progress achieved to date and requested clarification on the role of the caBIG™. Dr. Doroshow explained that it will take between 3 to 5 years to populate a database with information from all NCI-funded trials that includes all of NCI's mechanisms. A discussion ensued about garnering consensus on the adoption and use of a single software system, perhaps spearheaded by the CTWG, for use in all Cancer Centers. Dr. Cowan noted that Cancer Centers are choosing different public vendors and is costly for small centers. Dr. Niederhuber said that caBIG™ currently is holding a meeting with more than 1,000 people in attendance; Dr. Kenneth Buetow, Associate Director, Center for Bioinformatics and Information Technology, provided a software demonstration the night before, which illustrated that integration is possible between laboratory imaging, laboratory data, molecular data, and patient accrual, as well as information about the trial, data, and followup. Institutions may choose to use their own in-house or commercial software; the NCI is working to provide the connectivity between systems. Dr. Cowan noted that a common, Web-based clinical trials management system, which all of the Cancer Centers, SPOREs, and other groups could use, might allow everyone to enter patient data and enroll patients into studies quickly and easily. Dr. Barker mentioned that the NCI has been effective in helping the FDA build its electronic interface; the FDA plays an important role in the clinical trials process as well.

XII. ANNUAL TOBACCO CONTROL UPDATE—DRS. ROBERT CROYLE, MICHELE BLOCH, GEOFF FONG, AND MR. BILL CORR

Dr. Robert Croyle, Director, DCCPS, said that each year, the NCAB is provided with an update of the NCI's work in tobacco control and prevention research. This year, it was decided to broaden the discussion to global tobacco control research; Dr. Croyle acknowledged the interest and support of the John E. Fogarty International Center in this area. Dr. Croyle encouraged the NCAB members to provide feedback on these issues, even those with complex political and economic implications that are beyond the NCI's influence.

Dr. Croyle introduced the three speakers: Drs. Michele Bloch, Tobacco Control Research Branch (TCRB), DCCPS; Geoff Fong, University of Waterloo, Canada; and Mr. Bill Corr, Executive Director, Campaign for Tobacco Free Kids.

Reducing the Global Burden of Tobacco Use. Dr. Bloch said that, to help address the global burden of tobacco use, the NCI supports "The International Tobacco and Health Research and Capacity Building Program." Statistics from the World Health Organization (WHO) indicate that worldwide, just

under 5 million deaths per year currently are caused by tobacco use. That number is rising and is expected to reach 10 million by the year 2020, at which time tobacco will be the leading cause of death worldwide, with the greatest increases in deaths occurring in developing countries. In developed countries (i.e., those with high income), including the United States and the countries of Europe, the prevalence of smoking is slowly and steadily decreasing or is stagnant. In developing countries, with lower-middle levels of income, tobacco use is increasing. Women in developing countries have traditionally had very low levels of tobacco use because of cultural constraints against women smoking; it is an important public health opportunity to take advantage of this and preserve these low levels. Between 1970 and 2000, a dramatic and significant rise in global cigarette consumption occurred, culminating in nearly 6 trillion cigarettes consumed in 2000, three-quarters in developing nations. The Global Youth Tobacco Survey, which is a school-based survey of 13- to 15-year-olds conducted in more than 100 countries, indicates that 8.9 percent of students in this age group are cigarette smokers, with a far narrower difference between boys and girls, then between adult men and women. Other forms of tobacco, such as bidis, smokeless tobacco, and water pipes, are used by 11.2 percent of students in this age group.

Global tobacco use and mortality is growing and shifting from the developed to the developing world. It is anticipated that by approximately 2020, when about 10 million deaths are expected per year, 70 percent of these deaths will occur in developing nations. Tobacco use may kill as many as 1 billion people in the 21st century. Currently, approximately 1.4 million, or one in five, cancer deaths globally are attributed to tobacco use. Lung cancer is the leading cause of cancer death in men in both developed and developing countries. Breast cancer is the leading cause of cancer death in women, but in a growing number of developed countries lung cancer has surpassed breast cancer as the leading cause. Tobacco use also exerts a significant economic burden, particularly in poor countries among poor families. Some estimates indicate that 10 percent of family income is spent on tobacco use, which means less money for food, shelter, and education, leading to further decreases in family health.

This increase in tobacco use and mortality is occurring at a time when there is increasing recognition that health in developing nations is critically important for the economic development of these countries and also impacts global trade and stability. The health gains achieved from significant investment in preventing and treating infectious diseases such as HIV, malaria, and tuberculosis, and in childhood vaccinations may be reversed as tobacco use increases. Significant challenges to reducing tobacco use in developing countries exist, including the lack of public knowledge about the health hazards of smoking, other tobacco products, and secondhand smoke; financial and other barriers to increasing knowledge (such as low literacy rates); high rates of tobacco use and low rates of quitting among health professionals; and the large and growing presence of the tobacco industry in many of these countries.

An important development in global tobacco control has been the WHO Framework Convention on Tobacco Control (FCTC). The FCTC is an international treaty focused on addressing tobacco use, especially in the developing world. It was adopted unanimously by all WHO member states in 2003, and, currently, 143 nations have ratified the treaty, committing themselves to implementing its provisions. The FCTC includes measures to reduce the supply of tobacco, such as anti-smuggling measures, and also measures to reduce demand, such as price increases, advertising bans, and package warning labels.

NCI's involvement in the global tobacco and health research and capacity building program began in June 2001. The program is led by the John E. Fogarty International Center and consists of an RFA with the overall goal of addressing the burden of tobacco consumption in low- and middle-income nations by conducting research and building research capacity. The RFA requires that each application involve collaboration between a researcher in the United States and one or more researchers in a low or

middle-income country. In the first round of the RFA, 14 grants were provided to support research efforts in five countries in Latin America, 2 in Africa, 4 in Southeast Asia, 2 in the Eastern Mediterranean, and one each in Russia and China. Three grantee project publications were described at this meeting.

The first project involves a collaboration between researchers in the United States and at the Syrian Center for Tobacco Studies at the University of Aleppo in Syria. This research focuses on water pipe use, which is a traditional form of tobacco use in the Middle East and in parts of Asia and Africa. The research has identified common misperceptions about water pipe use, such as that water pipes are less dangerous than other forms of tobacco because the smoke is purified as it passes through water—there is, in fact, no evidence that this is the case. The carbon monoxide yields of the smoke from the water pipe are at least as high as that of cigarettes; in a typical water pipe session, the smoke produced has nicotine and tar levels approximately equivalent to that of a pack of cigarettes. There is evidence that water pipe use increases the risk of lung and other cancers, heart disease, and other pulmonary diseases. It use may also be a risk factor during pregnancy; this is important because many women in the Middle East smoke water pipes or may be exposed to the secondhand smoke produced by them.

The second project examines the economics of tobacco use in China. China is the world's largest tobacco consumer with 300 million cigarette smokers (66 percent of males smoke) and approximately 1 million tobacco-related deaths per year, conservatively. China also is the world's largest tobacco producer. The cigarette company in China is a state monopoly, thus, profits and taxes are returned directly to the central government and, in 2003 comprised 7.4 percent of the central government total revenue. The Chinese government is well aware of the financial benefits of tobacco use, but is much less aware of the large costs in both human and economic terms. Dr. Teh-wei Hu, Professor of Economics, University of California-Berkeley, together with colleagues at several Chinese universities, received a grant, in part, to perform a comprehensive estimate of smoking-related health care costs in China. They determined that approximately 3 percent of national health expenditures (approximately US$ 5 B) were attributed to smoking, in the form of direct health care costs, indirect morbidity costs and indirect mortality costs. They concluded that the adverse health effects of smoking exert a significant economic burden on Chinese societies. Dr. Hu and colleagues have published this research in both English and Chinese language journals; this research is already having an impact on tobacco control in China.

The third project involves research by Dr. Harry Lando, University of Minnesota, with colleagues in India and Indonesia, on Project Quit Tobacco International, which is an effort to implement cessation activities in developing countries of the world. India and Indonesia were chosen because these countries have a very high and growing prevalence of smoking, almost no quitting activity, and very high levels of tobacco use among health professionals. In their publication, they describe a roadmap for the implementation of cessation activities in countries where these activities do not exist. They describe their baseline data, the development of culturally appropriate materials, and the development of curricula for medical and nursing students. They discuss efforts to test these activities and to disseminate and raise the visibility of tobacco control and cessation efforts at the country level. This work has implications for the many developing countries in which cessation activities do not exist.

The benefits of this work will extend from low- and middle-income countries to the United States. These collaborations allow U.S. investigators to gain experience working in low- and middle-income nations, which lays the groundwork for other international cancer research activities that may involve these countries. Additionally, the lessons learned in resource-poor communities outside the United States may well be applicable for use in resource-poor communities in the United States. Because the United States is culturally diverse, a better understanding of the socio-cultural aspects of tobacco use around the world also will be useful within the United States. Lastly, because the tobacco industry operates as a global enterprise, utilizing many of the same strategies in the U.S. that it does in other

countries, international tobacco control research allows for global sharing of strategies and lessons learned. Recently, the Institute of Medicine (IOM) has issued a report on cancer control opportunities in low- and middle-income nations, in which it encourages U.S. researchers to undertake collaborative research of relevance to low- and middle-income countries; this RFA is a good example of exactly the type of work recommended by the IOM. NCI's continued investment in this area will be a major contribution toward reducing the global burden of tobacco use.

Questions and Answers

Dr. Runowicz asked whether, given that China profits significantly from tobacco sales, the Chinese government has any interest in cessation activities. Dr. Bloch explained that Dr. Hu's research will demonstrate to the Chinese government the human and health care costs associated with tobacco use. Also, as China industrializes and develops a more diverse economic base, the contribution of tobacco to central government funds will decrease and the importance of the human and health care costs will increase. She added that the health care cost estimates are conservative and likely are higher than reported in this research. Dr. Fong commented that, in the near future, health care costs associated with tobacco use in China will increase drastically as the population ages and smokes for a longer period of time.

Dr. Chabner asked for the number of countries that have ratified the FCTC and whether the United States has ratified this treaty. Dr. Bloch answered that 143 countries have ratified the treaty, but the United States has not. She deferred a question concerning active movements to ratify the treaty in the United States to Mr. Corr. Dr. Chabner asked about the percentage of tobacco (mainly cigarettes) consumed worldwide, particularly in China, that is supplied by American tobacco companies. Dr. Bloch speculated that a low percent of American tobacco is consumed in China. There are four or five transnational tobacco companies, including Philip Morris, British American Tobacco, and Japan Tobacco, which now owns RJR International.

Dr. Coffey asked whether China was sharing the costs of the research discussed at this meeting. Dr. Bloch answered that for this grant, the NIH provides all funding. Dr. Chen asked whether the Chinese government has any incentive to control tobacco use and why the United States is involved in this effort. Dr. Croyle answered that, currently, discussions with China focus on epidemiological projections concerning lung cancer incidences and mortality rates expected in 20 to 30 years. The scientific and health care communities in China are aware that lung cancer and other tobacco-related morbidities will be a significant problem in the future, and this awareness is beginning to impact policy considerations in China.

International Tobacco Control Policy Evaluation Project. Dr. Fong said that the human element implicit in tobacco use must be considered in tobacco use research and cancer prevention and control initiatives. As stated in the WHO Zeltner Report, "Tobacco use is unlike other threats to global health. Infectious diseases do not employ multinational public relations firms. There are no front groups to promote the spread of cholera; mosquitoes have no lobbyists." Cigarette companies have been very successful with advertising their products; tobacco advertising is pervasive throughout the world. Tobacco deaths have increased steadily since the 1950s; thus, the major question in global health terms is whether the upward trajectory of tobacco deaths can be flattened or turned downward. Large-scale, population-level interventions will be needed to achieve this change. The FCTC seeks to develop and implement mechanisms needed to reduce tobacco-related deaths. Some of the provisions of the FCTC address issues such as packaging and labeling, warning labels, elimination of misleading descriptors such as "light" and "mild," advertising, promotion and sponsorship bans or restrictions, protection from

exposure to tobacco smoke, price and taxation measures, and dependence and cessation education, communication, and awareness.

The potential impact of policies on the rates of tobacco-related deaths will depend on the intervention itself and also the size of the intervention and the length of implementation. An intervention implemented widely and for a significant length of time will have a larger impact. Thus, implementing policies that are strong and of lasting value will help reduce the number of tobacco-related deaths. The FCTC is described as an evidence-based, science-based treaty, but more research is needed to determine the effectiveness of various interventions. The FCTC provides an opportunity to study population-based interventions in many countries and the chance to measure the impact of policy changes and determine causal mechanisms. It also provides an opportunity to further develop the evidence base to inform the creation of effective tobacco control policies throughout the world.

Evaluating policies is challenging. Evaluation of national-level policies requires international studies with common methods and measures across countries that focus on the impact of policies on the individual. The influence of various forces on tobacco usage and quitting at the individual level must be assessed through cohort studies. The International Tobacco Control Policy Evaluation (ITC) project was created to evaluate tobacco control policies. Projects are underway in 13 countries encompassing approximately 70 percent of the world's population. The ITC project is conducting surveys to rigorously evaluate FCTC policies and to understand how and why a given policy works. For example, the impact of different types of warning labels on smoking knowledge and behaviors recently was evaluated. Canadian law requires larger and more graphic warning labels on cigarette packages than those required by most other countries, including the United States. These labels create a larger visual impact at the point of display or sale. Evaluation of warning labels in several countries showed that the larger labels enhance label noticing, or salience. The larger labels also increased the likelihood that people would think about the health risks of smoking. Larger labels increased knowledge about a specific adverse effect of cigarette smoking such as, for example, impotence. Moreover, this research found that there is a link between thinking about the information given on labels and the risks of smoking, which makes it more likely that the smoker will attempt to and successfully quit.

Population-level interventions are needed to fight the growing tobacco epidemic. The FCTC provides an important opportunity for research and using the results of this research to inform policy. Research supported by the NCI is helping to increase the evidence base for future U.S. tobacco control efforts.

Questions and Answers

Dr. Everson asked whether efforts were underway to require more graphic labeling on cigarette packages in the United States. Dr. Croyle deferred this question to Mr. Corr.

Opportunities for Tobacco Prevention and Cessation. Mr. Corr explained that the Campaign for Tobacco Free Kids is a privately funded, nonprofit national advocacy organization that works at the international, national, state, and local levels. The mission of the Campaign is to prevent young people from starting smoking, help adults quit, and protect everyone from secondhand smoke. Tobacco use in the United States, especially in the young, is unacceptably high; 4,000 children each day try a cigarette for the first time and more than 1,000 become daily smokers. Given that 90 percent of long-term smokers start as young people, reducing tobacco use among the young is an important issue. Progress has been made in reversing the levels of tobacco use in the country, and proven strategies have been developed that will and do reduce tobacco use. These strategies, however, must compete with a tobacco industry that

spends more than $15 B each year in promotion and marketing and constantly adapts its product and strategies to negate public policy and circumvent prevention and cessation efforts.

The NCI has played a critical role in building the knowledge base for tobacco prevention, cessation, and control, and it is critical that the NCI continue in that capacity. Population-based policies that are being implemented at the state and local levels are reducing tobacco use. For example, there is solid evidence that increasing the price of tobacco by 10 percent results in a 7 percent decline in youth prevalence and a 2 percent decline in adult prevalence. A number of states have recently increased their cigarette excise taxes, including Texas, Montana, Michigan, Washington, and Oklahoma. The tobacco industry, however, is offsetting the impact of these price increases; two-thirds of their $15 B in promotions is going into price promotions that, in effect, reduce the cost of tobacco.

Smoke-free laws are another strategy that not only protects people from secondhand smoke but also prompts smokers to try to quit, increases the number of successful quit attempts, reduces the number of cigarettes that continuing smokers consume, and discourages children from starting. In 2000, the U.S. Surgeon General stated that secondhand smoke laws decrease daily tobacco consumption and increase smoking cessation. Numerous states, cities and towns have now passed smoke-free laws. A question that remains is whether cessation treatment options, such as medications, counseling, and combinations of these services, are established to help smokers who have been prompted by smoke-free laws to try to quit smoking.

NCI-funded research on community-based programs has provided information concerning resources and activities necessary to reduce tobacco use at the community level. Statewide tobacco prevention and cessation programs have produced results. In Maine, for example, there has been a 59 percent reduction in the number of high school students who smoke in the past 8 years; in Mississippi, a 48 percent reduction; and in Oregon, a 51 percent reduction. These are dramatic results that should be continued, but state legislators responsible for appropriations need more and better evidence to justify continuation of these policies and to assure taxpayers that funds are being appropriately and effectively spent. Concerning funding, the states have collected $21.7 B in 2007 from the tobacco settlement and tobacco taxes. The Center for Disease Control and Prevention's (CDC) minimum prevention spending is $1.6 B.

Providing the FDA with the authority to regulate tobacco products is another strategy for the reduction of tobacco use. FDA product review mandates that no new ingredients can be added to a product unless they are generally recognized as safe. Cigarettes are not subject to product review, ingredient review, or ingredient disclosure. Cigarette advertisements from the 1960s and 1970s, which claimed that low tar and low nicotine products protected smokers' health, and current claims, such as "reduced carcinogens and premium taste," emphasize the need for FDA regulation of tobacco products. Other products that contain nicotine (such as nicotine gums and patches) are already regulated by the FDA, but tobacco products are not. Legislation has been introduced in both the Senate and House of Representatives that will give the FDA the authority to prohibit marketing that influences youth and misleads adults. The FDA also will have product regulation authority over tobacco products; reduced risk claims will need to be science-based and proved to the FDA. New health warnings will be added to packages, misleading terms like "light" and "low tar" will be eliminated, as will candy and other flavorings. States will be allowed to restrict and/or ban when, where, and how tobacco products are advertised. Similar legislation passed in the Senate in 2004 with 75 votes; the Campaign for Tobacco Free Kids is confident that the new legislation will pass in both houses of Congress.

The U.S. Department of Justice (DoJ) has pursued a lawsuit against major cigarette companies. The Campaign for Tobacco Free Kids, along with other public health organizations, asked the court for

permission to present to the court remedies important for public health; this request was granted. A 1,700-page decision was issued in 2006, which found that the companies have engaged in a 50-year fraud that is continuing to the present and is likely to continue into the future. The lawsuit will be on appeal for several more years, but if successful, the settlement could provide up to $4.8 B per year for cessation treatment; free medication, free counseling, and fully funded quit lines would be available to all adults who wish to quit smoking. Approximately $600 M would be available to fund public education campaigns focused on young people and debunking myths such as those about the safety of low tar and light cigarettes. Significant prohibitions on the industry's behavior would limit attempts to deter smokers from quitting and misleading the public.

The Campaign for Tobacco Free Kids would like the NCAB to challenge the NCI to understand the impact that population-based policies are having and to improve the knowledge base concerning these activities. More research is needed to build on current success regarding decreasing the use of tobacco products. The U.S. government and the private sector should work to build a better knowledge base to ensure that resources available at the state level and those received through the lawsuit will be put to best use and dramatically reduce tobacco use, disease, and death.

Questions and Answers

Dr. Chabner suggested that the NCAB develop a statement expressing the will of the Board to support tobacco control efforts in the United States, recognizing that tobacco use represents a significant threat to U.S. health and also is a growing international health threat. The NCAB should take the lead in the United States to control tobacco use through the support of tobacco regulations and support for NCI's investment in studying ways to implement population-based control methods. The NCAB also should support the ratification of the FCTC treaty.

Dr. Coffey commented that it has been difficult to develop a solid evidence base of interventions that work to reduce smoking. He noted that, in his opinion, package labels do not have a large impact on smoking levels, but acknowledged that advertisement bans, tax and price increases, and mandating smoke-free environments appear to have been successful. He added that he would be more enthusiastic about sharing research efforts with countries that begin to implement bans, such as on advertisements and on smoking in certain environments. He expressed skepticism that the Chinese government, for example, with its support of the tobacco industry, would be very supportive of implementing tobacco control policies. Because research funds are limited, they must be spent in ways most likely to have an effect. Dr. Fong noted that under the FCTC, countries are required to implement taxes and price increases. The goal of this project is to provide an evidence base that will permit countries to choose policies most likely to have an effect. Dr. Coffey emphasized that he wanted to ensure that research funds were not spent on approaches that were less likely to be effective. He said that the focus should be on policies that have been proven to work and on research that will allow the effective implementation of those policies throughout the world.

Dr. Chabner suggested that the NCAB should declare its position regarding the ratification of the FCTC treaty. Dr. Coffey asked about the amount of money that the NCI spends on tobacco control programs and research. Dr. Croyle commented that international projects constitute a small proportion of the tobacco control research budget. Dr. Cathy Backinger, TCRB, DCCPS, related that TCRB's extramural portfolio supports approximately $50 M worth of research. Dr. Croyle noted that the NCI is one of many funders of international tobacco control research efforts, and that funding from other foundations and governments outweighs NCI funding. Dr. Runowicz concluded by commenting that the NCAB is strongly supportive of the issues discussed today and encourages this work to continue.

A member of the NCAB made the suggestion that the NIH should not fund research grants at institutions that accept funds from the tobacco industry.

XIII. STATUS REPORT: THE CANCER GENOME ATLAS AWARDS—DR. ANNA BARKER

Dr. Barker provided an update on TCGA, a 3-year pilot project co-sponsored by the NCI and NHGRI to increase the comprehensive understanding of the genetic basis of cancer. Dr. Renato Dulbecco, Salk Institute for Biological Sciences, explained in an article that cancer cannot be sorted out until it is known what the human genome looks like. It is anticipated that TCGA's integrated database of molecular and clinical information will provide scientists with unprecedented opportunities to discover and develop a new generation of targeted diagnostics, therapies, and preventives for cancer. The enabling rationale for this project was based on work conducted by the Human Genome Project, the current knowledge of gene families and pathways, robust genomic analysis technologies, and the Sanger Project's experience in sequencing known genes (e.g., kinases are druggable). In addition, there have been a number of early indications that somatic mutations are important potential targets.

Dr. Barker described TCGA development milestones, such as the NCAB *Ad Hoc* Committee formed in 2003, and detailed the progress made in 2006 and 2007. In 2006, the NCI issued and funded the Biospecimen Core Resources (BCR) RFP and the Cancer Genome Characterization Centers (CGCCs) RFA, and held a Data Release Workshop. Tumor types—specifically glioblastoma, lung, and ovarian—were selected in September, based in part on existing samples and their location. Additionally, the NHGRI funded the Genome Sequencing Centers (GSCs). In December, the first TCGA Steering Committee meeting occurred, with a mixture of experts from the genome sequencing culture and cancer biologists, who gained a better appreciation for each other's roles in the effort. In March and April, it is expected that the BCR project will distribute tumor biomolecules to the GSCs and CGCCs, which will perform sequencing and characterization of the tumor biomolecules. The first set of TCGA data is scheduled to be deposited into public databases in May 2007.

There are four principal components of TCGA: the BCR project, CGCCs, GSCs, and the Data Coordinating Center. The BCR project obtains samples and conducts a pathologic quality control (QC) review of them. It is responsible for the central processing of specimens and tracks and performs quality assurance (QA) of all specimen-related operations, including informed consent. The project provides "standard" samples for technology platform comparisons and develops (with the Office of Biorepositories and Biospecimen Research) and monitors standard operating procedures for prospective specimen collection. It also serves as a member of TCGA's Steering Committee. CGCCs represent technology platforms for high-throughput genome characterization, including expression profiling, copy number changes, and DNA methylation (epigenomics). They are charged with improving existing technologies and releasing real-time data into a public database. High-throughput GSCs work on sequencing a large number of targets from the three tumor types and developing and integrating sequencing technologies. The Data Coordinating Center provides a platform for data collection and management, which will track data and ensure that it meets quality standards. It also will make TCGA data publicly accessible; scientists will have access to the data. Access to all TCGA data will be provided in a manner that meets the highest standards for protection and respect of the research participants. These TCGA components exist across the United States and include the members of the International Genomics Consortium (i.e., the BCR). The procurement process for tissue donors was completed in 2006 and includes: the Gynecologic Oncology Group (GOG) for ovarian; CALGB for lung; and the M.D. Anderson Cancer Center for glioblastoma specimens.

The project centers around the extraction of biomolecules from biospecimens, and the work is performed by the GSCs and CGCCs on biomolecules. It is integrated closely with the patient community;

NCI's DCLG has created a presentation for patient education. This is important, as personalized medicine will depend on the availability of patient samples, and prospectively TCGA will need to discuss relevant issues with patients, including genomic databases, sequencing, and real and potential risks. The R01 community and scientists—including SPOREs, the Mouse Models Consortium, or other groups—will be involved in analyzing the data.

Glioblastoma is ideal for TCGA study, as it is a "homogenous" tumor and has only one grade (highest) of a single histological type of cancer. It also has few other cell types, such as stromal or inflammatory cells, which might contribute non-tumor DNA to the extracted biomolecules. Genetic defects in glioblastoma tumors suggest therapeutic interventions. Dr. Barker noted several interesting classes and agents that are being developed around some of the genes that have been found during the last 3 to 4 years. Target selection will involve the identification of known cancer genes, integration of all cancer gene databases, and selection of a small number of genes (starting with no more than 500) to begin sequencing in glioblastoma samples. A meeting will be held with glioblastoma experts to discuss a strategy to identify new genes from TCGA's CGCCs. Another meeting will occur with NCI's other programs to begin data interrogation processes.

Informed consent and access to data remain key issues. TCGA's informed consent form is lengthy and detailed. It involves permission for: detailed genomic research; broad future research use of samples and health information; and placement of genomic and health information in widely accessible databases, with limitations. TCGA is sensitive to the risks that can be associated with the loss of privacy and issues related to the withdrawal of data and samples, as well as the potential benefits for future cancer patients. To capitalize on the potential for progress against disease and ensure privacy protection, TCGA will provide two levels of data access: one open and another that is controlled by passwords. Solving the issues of data access while remaining sensitive to patient protection likely will require genetic privacy legislation.

The 3-year timeline established for TCGA includes: the completion of genomic analysis of the three tumors; the ability to find and specify genomic alterations in genes associated with cancer; the ability to differentiate tumor subtypes based on genomic alterations; and the establishment of a genomics database that scientists can access.

Dr. Barker concluded with TCGA's potential impact, such as the identification of somatic changes in cancer genomes that could establish the molecular basis for each cancer and inform and enable a new era of molecular oncology; a molecular taxonomy of cancer; new molecular targets for diagnostics, therapeutics, and preventives; and an improved ability to stratify patients for clinical trials. NCAB members were referred to TCGA's Web Site, http://cancergenome.nih.gov, for further information.

Questions and Answers

Ms. Giusti asked whether the intent is to start with untreated patients who are then followed longitudinally. She cautioned against releasing the best samples first, and noted the difficulty in establishing a public portal. Dr. Barker said that the project is commencing with retrospective specimen collections and eventually will collect samples prospectively. Three levels of data access for this project are expected: 1) publicly available data, which will be de-identified; 2) data that are limited to R01 and other investigators; and 3) access for physicians who have donated samples. Dr. Danielle Gearhart added that a test run of the procedures was conducted to ensure that all of the biomolecules were of high quality.

Dr. Coffey asked about the percentage of the effort that will advance epigenetics, noting that epigenetics characterized a number of genetic changes, particularly methylation, found in prostate cancer. Dr. Barker replied that TCGA is a high-throughput project that has been designed to look at somatic cell

mutations; the project possibly could empower an epigenomics project. Dr. Carolyn Compton, Director, Office of Biorepositories and Biospecimen Research (OBBR), OD, added that a specimen-limited study approach is being used, and that blood is serving as the normal cell type. Blood is a good control for somatic genomics but not for epigenomic studies. In the three tumors selected, the serious cyst adenomas usually encompass the entire organ, and there are no normal cells remaining in the organ. Dr. Compton added that the limiting factor for tumor selection was site-matched normal cells.

XIV. 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 ~~w~~as affirmed by all serving Board members present. During the closed session of the meeting, a total of 1,984 applications were reviewed requesting support of $583,622,060.

XV. 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 141st regular meeting of the NCAB was adjourned at 5:00 p.m. on Tuesday, February 6, 2007.