DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
138th NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
June 14, 2006

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 138th regular meeting on Wednesday, June 14, 2006, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Wednesday, June 14, 2006, from 8:00 a.m. to 4:45 p.m. The meeting was closed to the public from 4:45 p.m. until adjournment at 5:30 p.m. NCAB Acting 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 (Acting Chair)
Dr. Samir Abu-Ghazaleh
Dr. James O. Armitage
Dr. Moon S. Chen, Jr.
Dr. Kenneth Cowan
Dr. Jean B. deKernion
Dr. Ralph S. Freedman
Ms. Kathryn Giusti
Mr. David Koch (absent)
Dr. Eric S. Lander (absent)
Dr. Diana M. Lopez
Dr. Arthur Nienhuis (absent)
Dr. Franklyn G. Prendergast
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. Michael Babich, CPSC
Dr. Louisa Chapman, OSTP (absent)
Dr. Allen Dearry, NIEHS (absent)
Ms. Raye Ann Dorn, VHA (absent)
Dr. Raynard Kington, NIH (absent)
Dr. Peter Kirchner, DOE
Dr. Richard Pazdur, FDA
Dr. John F. Potter, DOD
Dr. R. Julian Preston, EPA (absent)
Dr. Anita Schill, NIOSH (absent)
Dr. Donald Wright, OSHA (absent)

Members, Executive Committee, National Cancer Institute, NIH

Dr. John Niederhuber, Acting Director, Chief Operating Officer and Deputy Director for Translational and Clinical Sciences, National Cancer Institute
Dr. Anna Barker, Deputy Director for Strategic Scientific Initiatives
Dr. Kenneth Buetow, Associate Director, Center for Bioinformatics and Information Technology
Ms. Nelvis Castro, Deputy Director, Office of Communications
Dr. Mark Clanton, Deputy Director for Health Care Delivery
Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences
Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis
Dr. Gregory Downing, Director, Office of Technology and Industrial Relations
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
Mr. John Hartinger, Associate Director, Office of Budget and Financial Management
Dr. Ernest T. Hawk, Director, Office of Centers, Training and Resources
Dr. Thomas Hooven, Deputy Director for Management
Dr. Alan Rabson, Deputy Director, Office of the Director
Dr. Dinah Singer, Director, Division of Cancer Biology
Dr. Sanya Springfield, Acting Associate Director, Center to Reduce Cancer Health Disparities
Dr. Robert Wiltrout, Director, Center for Cancer Research
Ms. Sandy Koeneman, Executive Secretary, Office of the Director

Liaison Representatives

Ms. Suanna Bruinooge, American Society of Clinical Oncology
Ms. Roshundd Drummond, American Society of Therapeutic Radiology and Oncology
Dr. Margaret Foti, American Association for Cancer Research
Dr. Robert W. Frelick, Association of Community Cancer Centers
Dr. Monica Leibert, American Urologic Association
Mr. Douglas Ulman, National Cancer Institute, Director's Consumer Liaison Group
Ms. Karen Stanley, Oncology Nursing Society
Ms. Mary Mitchell, American Society of Therapeutic Radiology and Oncology
Dr. Clare O'Connor, National Science Foundation
Ms. Nancy O'Reilly, The American College of Obstetricians and Gynecologists
Ms. Barbara Stewart, Association of American Cancer Institutes
Ms. Julie Taylor, American Society of Clinical Oncology
Ms. Marie Zinninger, American College of Radiology

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I. CALL TO ORDER, OPENING REMARKS, AND APPROVAL OF MINUTES—DR. CAROLYN D. RUNOWICZ

Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, Farmington, CT, called to order the 138th NCAB meeting. She welcomed members of the Board, the President's Cancer Panel, *ex officio* members of the Board, staff, and guests. 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 then reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations. Dr. Runowicz thanked all patients and scientists and reminded members that NCAB members are representing them and have an obligation to continue to do so in all matters that come before the Board.

Motion. A motion was made to approve the minutes of the February 7, 2006, NCAB meeting. The motion was seconded, and the Board unanimously approved the minutes.

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

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

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

Dr. LaSalle Leffall, Jr., Charles R. Drew Professor of Surgery, Howard University Hospital, announced that the Panel's 2005-2006 annual report entitled Assessing Progress, Advancing Change has been delivered to the President. The report addresses high-priority recommendations the Panel previously made to the President and Congress regarding survivorship issues and translating research into cancer care. It was released formally to the public on June 2 at a press conference held at the 42nd annual meeting of the American Society of Clinical Oncology (ASCO). The Panel also hosted two educational sessions at the ASCO meeting to further address issues raised in the report. The first, moderated by Dr. Leffall, addressed challenges in cancer survivorship and included as panelists Dr. Carolyn Runowicz, President, American Cancer Society; Mr. Doug Ulman, Chief Mission Officer, Lance Armstrong Foundation (LAF); and Dr. Linda Jacobs, Coordinator, Living Well After Cancer Program, University of Pennsylvania. The second panel, moderated by Dr. Margaret Kripke, member of the President's Cancer Panel, addressed challenges in translating research and included as panelists Dr. Jon Kerner, Deputy Director for Research Dissemination and Diffusion, Division of Cancer Control and Population Sciences (DCCPS), NCI; Dr. Richard Pazdur, Director, Office of Oncology Drug Products, Food and Drug Administration (FDA); and Dr. William Galey, Director, Graduate and Medical Education Programs, Howard Hughes Medical Institute.

In addition to highlighting progress made in the areas of survivorship and translating research, the Panel's report addresses overarching issues that permeate and impact the cancer community. These overarching issues are fiscal constraints, health care coverage, education and communication, and coordination. Dr. Leffall noted that, although these issues are not new, they are pervasive at a time when the number of people diagnosed with cancer is growing, given the demographics of the aging U.S. population.

From the oncologists who cannot obtain full reimbursement for providing cancer care to the high cost of drug development, fiscal constraints are felt across the cancer continuum. Stakeholders in cancer care and cancer research must work creatively and collaboratively to make the most of available resources. Dr. Leffall stated that the Panel believes comprehensive health care reform is needed to address the current situation in which an estimated 46 million people in the United States lack health insurance of any kind and many millions more are underinsured for the cost of initial and ongoing cancer care. In the area of education and communication, there is a need to improve public understanding about cancer and the importance of cancer research. Equally critical is the need to educate

providers and patients about new findings, technologies, and available resources. Finally, the lack of adequate coordination of cancer resources has been raised repeatedly by the Panel. Without coordination, there is the risk of spending shrinking resources on redundant or incompatible activities and creating proprietary issues that later can become obstacles to progress. Dr. Leffall noted that the Panel believes that the diverse stakeholders in the cancer community must find more effective and efficient ways to communicate and collaborate to accelerate advancements across the cancer research and cancer care enterprises.

Looking forward, Dr. Leffall reported that the Panel is in the process of planning its next series of meetings entitled "Promoting Healthy Lifestyles to Reduce the Risk of Cancer." This 2006-2007 series of four meetings will focus on ways to reduce cancer incidence and mortality through the promotion of healthy lifestyles. Areas of particular interest will include the impact of tobacco use, environmental tobacco smoke, obesity, physical activity, and nutrition on the risk of developing cancer. Two of the meetings will focus on obesity, physical activity, and nutrition and the other two on tobacco issues. The meeting dates and locations are: (1) September 11, 2006, in Minneapolis, MN; (2) October 23, 2006, in Lexington, KY; (3) December 5, 2006, in Portland, OR; and (4) February 12, 2007, in Jackson, MS. The proposed structure of the meetings will be to focus the first half of the day on current scientific research in a particular area. During the second half of each day, the Panel will hear and learn about model programs relevant to healthy lifestyles and cancer risk reduction. Dr. Runowicz commented on the importance of the Panel's move to the areas of obesity, nutrition, and lifestyle because partnering with other organizations to fight this epidemic can have an impact on cancer prevention, incidence, and mortality.

IV. NCI ACTING DIRECTOR'S REPORT—DR. JOHN NIEDERHUBER

Dr. John Niederhuber, Acting Director, NCI, informed members that, although progress appears slow and snail paced, the decline in U.S. death trends for cancer of all sites in the past few years reflects progress related to mortality and hope for the future. Dr. Niederhuber then presented an update of the NCI budget status for the fourth quarter of Fiscal Year (FY) 2006. He noted that: (1) the budget was subject to mid-year taps of almost $4 M for direct utility costs to the NIH; (2) the Research Project Grants (RPG) payline is at about the 11th percentile, with about 15 percent of the competing pool in reserve for exceptions; (3) Type 5 grants are being funded at about 2.35 percent below the commitment of record; (4) Special Programs of Research Excellence (SPOREs) are 2 percent below FY 2005, and the Cancer Centers line is essentially flat with FY 2005; and (5) the Training line is 1 percent above FY 2005. Dr. Niederhuber noted that conversations have been held with Cancer Center directors, but no one solution to the Centers budgeting process has been identified.

Honors. Dr. Niederhuber called attention to honors received by NCI staff: (1) Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics (DCEG), received the Medal of Honor from the International Agency for Research on Cancer; (2) Dr. Mitchell Gail, Chief of Biostatistics Branch, DCEG, received the Marvin Zelen Leadership Award in Statistical Science; (3) Dr. Dolph Hatfield, Chief, Molecular Biology of Selenium Section, Center for Cancer Research (CCR), received the Outstanding Mentor Award; and (4) Dr. Carl Wu, Chief, Laboratory of Molecular Cell Biology, CCR, was elected to the National Academy of Science (NAS). In addition, the NCI's Cancer Bioinformatics Grid (caBIG™) has received *Computerworld* magazine's 21st Century Achievement Award—Science.

Personnel. Dr. Niederhuber reported on recent intramural staff changes and staffing for the newly created Coordinating Center for Clinical Trials. Appointments included: (1) Dr. Paul Meltzer as Chief, Genetics Branch, and Head, Clinical Molecular Profiling Core, CCR; (2) Dr. Margaret Tucker as Director, Human Genetics Program, DCEG; and (3) Dr. Mark Udey as Deputy Director, CCR. Those receiving tenure at CCR were: (1) Dr. Philip Dennis, Medical Oncology Branch and Affiliates; (2) Dr. Steven Hou, Mouse Cancer Genetics Program; (3) Dr. Steven Libutti, Surgery Branch; and (4) Dr. Stanley Lipkowitz, Laboratory of Cellular and Molecular Biology. Director for the Coordinating Center for Clinical Trials is Dr. Sheila Prindiville, and Program Directors are Drs. Deborah Jaffe, LeeAnn Jensen, and Ray Petryshyn.

Update: Trans-NIH and NCI Programs. Members were reminded that the Trans-NIH Angiogenesis Research Program (TARP), in which the NCI plays a significant leadership role, is growing steadily both in individuals across the NIH joining the research program, and in Institutes that have added their activity to this trans-NIH program. The TARP and a program in the area of biomarkers, also with strong NCI involvement, were recommended to be among the portfolio of trans-NIH programs to be used by Dr. Elias Zerhouni, Director, NIH, in advocating for the NIH budget as the FY 2008 process begins. Other trans-NIH programs in the planning process are one for embryogenesis and cancer development and another regarding cancer stem cells and stem cell biology. Dr. Niederhuber stated that one goal is to develop programs within the NCI that cut across Divisions. Among these are the Lung Cancer Program, which evolved from the NCI's Integration and Implementation (I2) Strategy Program, and the Breast Cancer Stamp Premalignancy Research Program, which is funded by the NCI's share of the breast cancer stamp money. Dr. Niederhuber noted that the latter extends from laboratory work on breast cancer stem cells through imaging to translation in the NCI clinical programs. Other trans-NCI programs in discussion and planning stages are one in epidemiology and prevention and a second one in computational biology and biostatistics.

Cancer Center Directors' Retreat. Dr. Niederhuber reported that the Cancer Center Directors at their fall meeting in 2005 identified the need to have greater input into strategic priorities that they felt were necessary to advance toward the goal of reducing the burden of cancer in the United States. Subcommittees on prevention, early detection, treatment, survivorship, coordination and integration, and dissemination were formed. The Subcommittees have worked through the year to prepare a document that sets priorities within those areas and proposes strategies for achieving some of the goals. At the spring meeting of the Center Directors, a draft was developed, which will be finalized over the summer. The current plan is to present the document to the Subcommittee on Cancer Centers at the September NCAB meeting.

Director's Consumer Liaison Group (DCLG). Dr. Niederhuber announced that the DCLG, which is chaired by Mr. Ulman, will be holding a summit meeting for the cancer advocacy community on June 19-20 at the Natcher Conference Center. Poster sessions and other mechanisms are planned to present information about the scientific research in progress on the NIH campus and at the NCI.

Budget. Members were reminded that the FY 2007 President's budget, which includes $4.753 B for the NCI (a -0.8 percent change from FY 2006), has not yet been enacted and the prospect is that another Continuing Resolution will provide funding beyond September 30 until Congress acts on the legislation. Dr. Niederhuber then reviewed the source of the current stresses on the NCI budget. The 80 percent increase in the NCI budget from 1998 to 2003, a period which saw a doubling of the NIH budget, has been followed by essentially flat budgets in the ensuing years. National issues that are having an impact on the discretionary budget of the Federal Government include the deficit, defense and homeland security priority requirements, Katrina recovery, pandemic flu, and budget cuts (-2.7 percent for the Department of Health and Human Services [DHHS]). The impact of the decreases has been compounded by the Biomedical Research and Development Price Index (BRDPI), which is about 5.5 percent.

As a response to the perception by the extramural community that Requests for Applications (RFAs) and Program Announcements (PAs) took resources from the RPG pool during the near-doubling of the budget, Dr. Niederhuber presented data to show that NCI's unsolicited RPGs far outnumber the solicited grants, and that the percentages for both have been constant throughout that period and to date. Similarly, he noted that budgets for translational and basic R01-type research have remained essentially the same throughout the doubling process. Regarding the big projects initiated by the NCI, Dr. Niederhuber commented that progress in biomedical research for any disease can be traced back to the NCI investment in cancer as a model for understanding diseases. He expressed the view that the NCI has

an obligation to continue to lead and develop the enabling technologies that will allow R01 investigators to continue to be at the forefront in research.

Other pressures on the NCI budget include the fact that the doubling of the NIH budget contributed to the building of new facilities and an increase in the number of research faculty on the academic campuses. Dr. Niederhuber reminded members that the impact of that buildup would be seen in 2005-2006. As evidence of this, he pointed out that the number of competing **applicants** increased by 799 in the last 2 years compared with an increase of 962 during the 5 years of the NIH doubling and NCI near-doubling. NCI applicants have passed the 5,000 mark, and the number continues to increase. Similarly, the number of competing **applications** increased by 1,371 in the period of doubling compared with the increase of 1,076 in the last 2 years. Dr. Niederhuber noted that the change in the success rate has not been huge considering the dramatic increase in number of applications received and the current stresses on the budget. He presented a slide published recently in *The New England Journal of Medicine* showing the annualized growth of the NIH budget from 1971 to 2005 with greatly fluctuating highs and lows to illustrate the need for a strategic U.S. plan for support of biomedical research to promote the steady growth needed to keep the United States in the lead.

NCI Lung Cancer Program. Dr. Niederhuber reminded members that the Lung Integration and Implementation Team (Lung I2) was formed a few years previously to address concerns in the lung cancer community about the NCI commitment to lung cancer. He reminded members that the I2 Teams are structured to set priorities to begin to address concerns, find leadership to develop interest, identify people across the NCI and extramurally to participate in the research, and then transition to a more formal program. As a first step, the Lung I2 has formulated and submitted a series of recommended priorities for future research, together with estimates of the funding that would be needed. Dr. Niederhuber reported that a meeting was held in April to outline an implementation plan. The goal was to organize a structure for the allocation of NCI's resources toward lung cancer research on the basis of the Lung I2 recommendations. A follow-up teleconference was held in May with the Team to discuss progress, which included discussions with the FDA on a joint clinical trial, a meeting with Division of Cancer Biology (DCB) staff to begin planning for an RFA in cancer biology, and a meeting with trans-NCI lung investigators.

Dr. Niederhuber then briefly reviewed progress in the NCI Lung Cancer Program toward implementing the recommendations. In the area of governance, recruitment is underway for a senior clinician to oversee the program and coalesce and expand the expertise in the NCI. In addition, NCI's Cancer Intervention and Surveillance Modeling Network (CISNET) has received supplemental funding. In the area of early detection, the National Lung Screening Trial (NLST) biorepository has received additional funding to protect this tissue resource. In the area of drug development, the lung cancer biology RFA is in planning stages, and resources have been allocated toward a biomarkers trial in non-small cell lung cancer (NSCLC) and an early-phase epigenetic trial. In the area of imaging, novel imaging probes will be monitoring tumor uptake in the early-phase epigenetic trial. Regarding the recommendations in the area of tobacco control, Dr. Niederhuber stated that he informed the Lung I2 team that resources are not available beyond the 187 NCI-funded projects already underway and that the NCI would work to leverage outside resources for the recommended additional research in this area.

In the interest of time, Dr. Niederhuber postponed his research review except to note that the NCI is taking an active role, together with the DHHS, The White House, and Centers for Disease Control and Prevention (CDC) in developing U.S. policy related to the new human Papilloma virus (HPV) vaccine.

In Memoriam: Dr. Anita Roberts. Dr. Niederhuber concluded his report with a tribute to the life and work of Dr. Anita Roberts, Chief, Laboratory of Cell Regulation and Carcinogenesis, CCR, who died in May after a 2-year battle with gastric cancer.

Questions and Answers

Ms. Kathryn Giusti, CEO and Founder, Multiple Myeloma Research Foundation, Inc., observed that she is hearing from patients that hope is hard to find right now. She emphasized the importance of involving academia, the NCI, industry, and nonprofit and philanthropic organizations to communicate one cohesive message about the true nature of the current situation and exert pressure toward finding solutions to the current budget situation as it affects biomedical research. Dr. Runowicz commented that young investigators are becoming discouraged, and she expressed concern that, although the total number of applicants is increasing, there has been a 20 percent drop in the rate of the increase from the peak years. Ms. Giusti expressed the view that the problem should be addressed through parallel paths, with advocacy organizations both exerting pressure in Washington and raising awareness of the need for philanthropy for cancer in America. Dr. Anna Barker recalled that the last transition in science occurred in the mid-1990s when the quest to sequence the genome began. There was an unprecedented coming together of the scientific and advocacy communities in a massive march on the mall in 1998 and subsequent testimony that included the recommendation that the NCI budget be doubled. She noted that there are opportunities now for science and advocacy to come together in new ways to propel another transition in science for cancer patients. Dr. Niederhuber agreed with Ms. Giusti that other issues affect patients besides funding science and research. He expressed concern that scientific progress in prevention and treatment may be phenomenal but a greater risk factor for some will be the inability to access the prevention and treatment advances.

Dr. Moon Chen, Professor, Public Health Sciences, University of California, asked about the extent to which primary prevention of tobacco use will be emphasized in the new Lung Cancer Program. Dr. Niederhuber briefly described research on the AKT MTOR pathway that led to the development of at least five lead compounds that could be influential in the area of prevention, and he pointed out that much other intramural and NCI-funded prevention research is ongoing. Behavioral aspects of prevention are being addressed by working with other Institutes, other departments of the government, and extramural agencies to leverage resources in this restricted budgetary time.

V. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Policy, Analysis and Response (OPAR), reminded members that the President's Budget for FY 2007, which was announced on February 6, included $28.6 B for the NIH and $4.8 B for the NCI. The House of Representatives put forward the Labor, HHS, Education bill with essentially the same numbers. House action to date included a hearing on April 6 in which an NIH overview was presented, with Dr. Niederhuber participating. The bill was passed by the Subcommittee on June 7, and the full appropriations committee scheduled a hearing on June 13 and passed a bill. In the Senate, an overview hearing was held on May 19, but no other action is scheduled to date.

Ms. Erickson then highlighted some recent meetings and other events during which NCI staff had an opportunity to speak to and educate Congress on a variety of topics. Dr. Niederhuber and Dr. Raffit Hassan, CCR, participated in an April 3 briefing on the status of NCI research on mesothelioma before members of the Senate Judiciary Committee. On April 5, the Friends of Cancer Research and the American Association for Cancer Research (AACR) sponsored a briefing on Chemoprevention and Early Detection, featuring a panel of speakers. The briefing was attended by many congressional staffers. Dr. Anna Barker, Deputy Director for Advanced Technologies and Strategic Partnerships, Office of the

Director (OD), was one of the panelists and spoke about both the opportunities in chemoprevention and early detection and some of the barriers that could benefit from legislative action. On April 5, the U.S. Oncology and National Electrical Manufacturers Association sponsored a briefing on the role of imaging in cancer care. Dr. Dan Sullivan, Associate Director, Cancer Imaging Program, Division of Cancer Treatment and Diagnostics (DCTD), was one of the panelists. On April 12, Dr. Niederhuber and Dr. Joe Harford, Office of International Affairs, OD, participated in a briefing on the American Russian Cancer Alliance that had been requested by Rep. Steny Hoyer (D-MD). The participants were able to provide information on the status of this alliance, some of the accomplishments, and future plans. On May 1, Dr. Niederhuber participated in a second briefing on the Alliance at the request of Sen. Arlen Specter (R-PA).

Questions and Answers

Dr. Runowicz cited the successful development of an HPV vaccine as one of cancer research's successes and expressed the view that it should be part of an important message to Congress that many years passed between the basic science phase of the vaccine and its translational and, now, preventive application.

VI. DIRECTOR'S CONSUMER LIAISON GROUP REPORT—MR. DOUG ULMAN

Mr. Doug Ulman, Chair, DCLG, reminded members that the DCLG was established in 1997 as the first all-consumer advisory committee at the NIH; other Institutes have followed suite. Fifteen consumers were selected through a national nomination and review process and appointed by the Director, NCI, to provide an important link between the NCI and the advocate community. The DCLG is a chartered Federal Advisory Committee as are the NCAB and President's Cancer Panel. Consumer advocates are defined broadly as survivors of cancer or anyone who has been affected by the suffering and consequences or risk of cancer. DCLG membership, therefore, are cancer survivors, family members, caregivers, health care professionals, and consumer advocates, reflecting the breadth and diversity of the cancer consumer advocacy community.

As a chartered committee, the DCLG serves as a primary forum to discuss issues and concerns and exchange viewpoints that are important to the broad development of NCI program and research priorities. The DCLG provides recommendations to the Director, NCI, in response to specific advice and requests from the Director and in response to the needs of the cancer advocacy community. Strong collaborations are established and maintained between the NCI and the advocacy community to reach common goals. DCLG involvement in NCI programs and activities include: (1) attendance by the Chair at the NCI Budget Planning Retreat; (2) liaison with members of the Consumer Advocates in Research and Related Activities (CARRA), Office of Liaison (OLA), who are actively engaged in caBIG™; (3) representation on the Clinical Trials Advisory Committee; (4) representation on the External Scientific Committee of the Cancer Genome Atlas Project and participation in the Data Release Workshop held in May; and (5) collaboration with the OLA and Office of Cancer Survivorship on the Biennial Conference on Survivorship Research, where members help implement the Survivor/Research Mentoring Program.

As an example of the work of the DCLG, Mr. Ulman noted that several members have worked closely with Dr. Barker's office to adapt a PowerPoint presentation on the Cancer Genome Atlas Project for a broader lay audience. A dissemination plan is being formulated. He pointed out, also, that the DCLG has been a springboard to other positions within the Institute. He cited as examples Ms. Giusti, a former member who now serves on the NCAB, and Ms. Paula Kim, a former member who now serves on the NCI Board of Scientific Advisors (BSA).

Mr. Ulman explained that many of the current activities of the DCLG address the expressed needs of the advocacy community for more dialogue with the Institute. These activities include the *NCI Listens & Learns* Web Site (http://ncilistens.cancer.gov) and the upcoming advocates' summit—*Listening and Learning Together, Building a Bridge of Trust*—to be held on the NIH campus on June 19-20. Mr. Ulman noted that education and mobilization will be two focuses of the summit, as well as providing an opportunity for the far-flung groups to see the breadth and depth of the activity on the campus. A Town Hall Meeting hosted by the DCLG in the evening will be a more informal opportunity for advocates to provide direct feedback to the DCLG and the Institute. Five new members will be appointed in July to replace members whose terms have expired; more than 90 applications have been received. The DCLG has two in-person meetings per year and holds at least two meetings by teleconference. Currently, the DCLG has an Agenda Working Group, a Summit Planning Working Group, and an *NCI Listens & Learns* Working Group.

Mr. Ulman provided additional information about the Web Site. *NCI Listens & Learns* is an online dialogue among the NCI, the cancer-related advocacy community, and the general public. Questions are posted, for a 2-month period, from the various NCI Programs for discussion and feedback from the community. At the end of that time, the Programs respond, describing what use was made of the feedback. Mr. Ulman noted that it was determined early on that *NCI Listens & Learns* would be implemented as a pilot project; evaluation currently is underway and will be reported to the NCAB when that process is complete. In closing, Mr. Ulman stated that the next steps for the DCLG include continuing to forge new collaborations between the NCI and the cancer-advocacy/sponsorship community, and he welcomed suggestions in that regard from the NCAB. He noted that the DCLG is becoming more and more a part of the NCI culture and is open to suggestions as to how it can become even more involved. An annual update on the DCLG will be on a future NCAB agenda.

Questions and Answers

Ms. Giusti commented that the community advocates are more convincing when they can present specific data to back up their positions on the issues, for example, on the barriers that may exist. Because some have the data and others have education or voices, the need is for all to share the knowledge and become one voice. She applauded the work of the DCLG in helping to educate the advocacy community. Dr. Pazdur explained that the FDA has a large commitment to patient advocates, particularly in a program where patients consult on various applications and sit in on advisory committees as special government employees. He asked whether it would be possible to have some membership from the FDA Office of Special Health serve on the DCLG, either as members or *ex officio*, especially as the NCI/FDA interaction moves forward. He noted that there might be some common lessons between these two programs that could be mutually beneficial. Mr. Ulman replied in the affirmative, and Dr. Pazdur agreed to provide names of the candidates. Drs. Niederhuber and Barker commended Mr. Ulman's leadership of the DCLG, and Dr. Barker expressed the view that advocates will be increasingly instrumental in implementing personalized medicine, especially in terms of issues like tissue access, privacy, and informed consent.

VII. SPECIAL RECOGNITION OF RETIRING MEMBERS—DR. JOHN NIEDERHUBER

On behalf of the NCI, Dr. Niederhuber recognized and thanked five NCAB members whose terms of office are retiring as of this meeting. For each, he provided a brief description of their particular contributions to the NCI over and above their service on the NCAB. The retiring members are: Dr. Samir Abu-Ghazaleh, Director, Gynecology and Gynecologic Oncology, Avera McKennan Hospital and University Health Center and Avera Cancer Institute; Dr. James Armitage, Joe Shapiro Professor of Medicine, University of Nebraska College of Medicine; Dr. Ralph Freedman, Professor, Department of

Gynecologic Oncology, The University of Texas MD Anderson Cancer Center; Dr. Eric Lander, Director, Broad Institute of the Massachusetts Institute of Technology and Harvard Medical School; and Dr. Arthur Nienhuis, Director, St. Jude Children's Research Hospital.

VIII. NCI ALLIANCE FOR NANOTECHNOLOGY IN CANCER: RESEARCH ADVANCES AND DEVELOPMENT OF CLINICAL APPLICATIONS—DRS. ANNA BARKER AND PIOTR GRODZINSKI

Dr. Barker began her update of the NCI Alliance for Nanotechnology in Cancer by reminding members that initiatives like these generally begin as follow-ons to other programs and are funded by closing major programs that have become less productive or have reached the end of their useful life. In this particular case, funding was identified by ending the NCI Unconventional Innovations Program and a Biosensor Program with the National Aeronautics and Space Administration. She noted that three to four major breakthroughs have come out of the nanotechnology centers in less than 6 months of operation, discoveries that have the potential to make a difference for clinical research. She reminded members that nanotechnology occurs in the range of 10-100 nanometers, moving down in the cell beyond current levels, in terms of looking at mechanisms. This technology, more than any other, has the potential to be the key enabler for the transition of molecular-based science into the clinic. This particular area of technology promises to be effective across the whole continuum of discovery, development, and delivery.

Dr. Barker reviewed NCI's strategic approach to nanotechnology. Investment in novel technologies began with the Unconventional Innovations Program in 1998. Counsel on developing a cancer nanotechnology plan was sought from the scientific, cancer research, and advocacy communities. A comprehensive effort was planned to drive systems-level changes and catalyze product development and the Alliance was launched in 2004. The Cancer Nanotechnology Plan is available on the NCI Web Site (www.nano.cancer.gov). Execution of the plan is milestone-driven, with defined programs, collaborators, and reporting processes. Dr. Barker reported that every milestone has been met or exceeded to date. She stated that research goals are focused on bringing new tools to the clinic and practicing clinical oncologists as quickly as possible. New approaches to imaging and diagnostics promise to provide the kinds of platforms needed for the future, and there is evidence that nanotechnology will enable the real-time monitoring of patients.

Components of the Alliance include: (1) Centers of Cancer Nanotechnology Excellence (CCNEs); (2) Nanotechnology Platforms for Cancer Research, which complement the Centers by providing the latest technologies developed by the R01 community; (3) Multidisciplinary Research Teams, including a training program with the National Science Foundation (NSF); and (4) the one-of-a-kind, intramural Nanotechnology Characterization Laboratory (NCL), which developed assays to assess nanoparticle toxicity, pharmacology, and pharmacokinetics, setting the stage for FDA regulatory review. Dr. Barker noted that more nanotechnologies than expected are being submitted to the NCL for characterization, making it an effective approach that makes the best of the intramural program available to the extramural program. The eight Centers are disbursed geographically and will be connected virtually through caBIG™. Twelve Cancer Nanotechnology Platform Partnerships are associated with the Centers. In collaboration with the NSF, the NCI is training nanotechnology investigators for the future through programs entitled: (1) *Building Leadership for the Nanotechnology Workforce of Tomorrow* at the University of Washington, (2) *Integrative Nanoscience and Microsystems* at the University of New Mexico, (3) *Nanomedical Science and Technology* at Northeastern University, and (4) *NanoPharmaceutical Engineering and Science* at Rutgers University.

Dr. Barker pointed out that the NCI has reached out to its interagency collaborators to ensure that the program reaches its full potential. Collaborations include one with the FDA in the areas of training

and developing regulatory pathways for new nanotech interventions for cancer, and one with the National Institute for Standards and Technology (NIST) to address regulatory issues in the area of standards and precision measurement. In addition, the Alliance shares data and platforms with NIH programs. Dr. Barker expressed the view that the NCI, together with the NIH Nanomedicine Roadmap, is leading biomedicine, in terms of the National Nanotechnology Initiative. She briefly touched on the NCL's role in the Alliance. The NCL role is to interface with the CCNEs, individual investigators, the NIST, and the FDA to develop standards and characterization data for nanoscale materials; perform preclinical toxicology, pharmacology, and efficacy testing of nanoscale devices; and formulate and validate protocols for physical, *in vitro*, and absorption, distribution, metabolism, and excretion (ADME)/toxicity characteristics.

Dr. Barker stated that an attempt was made to have the organization of the Alliance reflect the sophistication of the science. Novel attributes include the steady interaction among Alliance participants and the community through: (1) a self-governing Governance Committee, with the NCI as an *ad hoc* member; (2) continual evaluation of project programs through performance milestones; (3) teleconferences; (4) Technology Transfer, Intellectual Property, and Communications Working Groups; (5) a Web site with "Knowledge Environment" and a secure intranet for Alliance members; and (6) advocacy involvement on an ongoing basis. Dr. Barker stated that the challenge for the Alliance is to produce tangible solutions that are clinically applicable in a short period of time. In this regard, many nanotechnology devices already are being used and several agents are in trials. She predicted that the area would move quickly because of the investment made across the United States and worldwide, and that there would be much commercial interest. She noted that the medical community expects significant advances where solutions are currently nonexistent and where replacement technologies are superior to existing methods. The Alliance is working to identify early successes and develop case studies to address the challenge of bringing these advanced technologies and oncologists together. The NCI is making an effort to ensure that all programs, but especially the Integrated Cancer Biology, Nanotechnology, and Proteomics Programs, are well interconnected. The challenge is to produce a paradigm change, and this is being done in an environment of constant education and information exchange.

Dr. Piotr Grodzinski, Program Director for Nanotechnology, OD, continued the progress report from the perspective of the nanotechnologies that are moving toward the clinic. He explained that those submitting proposals to the NCI Nanotechnology Program are required to be associated with an NCI-funded Cancer Center and have access not only to molecular biology and clinical departments, but also to physics and engineering departments. He pointed out that association with an existing Cancer Center addresses infrastructure needs, and multidepartmental involvement allows for a multidisciplinary environment. Interaction with other agencies also was stressed. The Cooperative Agreement mechanism was used, which called for the formation of the Governance Committee to provide oversight of the whole program. In selecting the CCNEs, attention was paid as to the institutions' strengths and weaknesses in terms of their technology involvement, as well as how their programs divide between the high-risk and evolutionary categories. Six program areas were chosen, and they are fairly well represented across the eight CCNEs. Attention was paid to the balance between high-risk, innovative programs and evolutionary projects of lower risk that may be more mature.

Following his introduction, Dr. Grodzinski presented brief snapshots, one from each CCNE, of recent developments in three areas: the sensing area, which can contribute to early diagnosis and recurrence monitoring; new contrast agents that rely on nanoparticle platforms and provide for high resolution; and targeted delivery of therapeutic drugs to the organ.

- At Northeastern University, CCNE researchers have developed a sensitive assay that can recognize both protein and nucleic acid. The advantages are that this assay can reach low

femtomolar and attomolar ranges of detection, and it is a diversified platform that allows the scientist to recognize a number of different signatures.

- In the area of early detection, the Emory/Georgia Tech Center has been using quantum dots as a label in multiplexed assays. Quantum dots are small semiconductor crystals with diameters in the 20-50 nanometer range, and emission wavelengths that can vary from blue through infrared. This laboratory has developed a three-color assay for recognition of the expression levels of proteins associated with breast cancer.
- The CCNE at Harvard University has developed an "intelligent" sensor that can work in the *in vivo* environment. The sensor involves the use of iron oxide nanoparticles decorated with polyethylene oxide (PEG) and provides an enhanced signal in magnetic resonance imaging (MRI) that makes it possible to sense the presence of the tumor.
- The CCNE at CalTech is working on a concept called "click chemistry" that allows for combinatorial synthesis in both small-volume and high-throughput environments. This technology involves the use of micro-fluidics, which are complex networks of channels built of polymer or glass material. This laboratory is using click chemistry for the development of a regulate-able probe for positron emission tomography (PET) imaging. The micro-fluidics approach allows for faster synthesis than is currently possible and the use of smaller volumes.
- At the Stanford University CCNE, researchers are developing another quantum dot approach that has the potential to move imaging techniques forward. This approach eliminates the need for external excitation of the quantum dot and makes it possible to image tissue that is deeper in the animal.
- The research team at the Washington University CCNE is working to develop techniques that target multiple organs. The team currently is using integrins to target angiogenesis. Potential applications would be imaging enhancement and targeted therapeutics delivery.
- Similarly, the team at the MIT/Harvard CCNE is working to improve local delivery using polymer-based particles that employ aptamers for targeting. The first demonstration of this technique showed significantly suppressed tumor growth in the xenografts mouse model when the technique was used to target prostate-specific membrane antigen.
- In a departure from the focus of the first seven CCNEs on applications and demonstrations of therapeutic efficacy and detection, CCNE researchers at the University of North Carolina have developed a reproducible and inexpensive method for manufacturing nanoparticles rapidly. The particles have been shown to be multifunctional. An attractive feature of this methodology is that a drug or contrast agent can be introduced into the mold prior to pouring the polymer, becoming part of the particle itself and eliminating the need for sophisticated attachment techniques.

Dr. Grodzinski then outlined achievement targets for the next year of the Alliance. In addition to the science and technology, bridges will be developed to build programs across the Centers. Strategies being considered toward this end include common data sharing and technology transfer. The caBIG™ community will be involved in the development of common strategies for data storage; interactive and compatible grids already are being formed. Dr. Grodzinski noted that the Alliance expects to move into the area of clinical application by means of a large statistical base of samples for bio-barcode assay and clinical trials of integrin-targeted nanoparticles being produced at the Washington University. The docetaxol studies in the xenografts mouse model at the MIT/Harvard CCNE will be expanded to studies in larger animals. In addition, plans are being made to commercialize the nanoparticle platform that was developed at the University of North Carolina.

Questions and Answers

Dr. Barker commented that the nanotechnology program is committed in commercializing these technologies. Each of the Centers has submitted a plan for partnerships for their respective technologies,

and several companies will emerge out of Alliance activities. She expressed the view that nanotechnology will be the transformative force in science for the next decade or so and that the NCI has been in the forefront of the movement, beginning with the Unconventional Innovations Program. She reported that an education session was presented by NCI staff to standing-room-only crowds at the past two annual meetings of the AACR. Dr. Jean deKernion, Professor and Chairman, Department of Urology, David Geffen School of Medicine at UCLA, asked whether a component of education or clinical correlation was included in the grants for the Centers. Dr. Grodzinski replied in the affirmative, noting that many of the Centers already are creating courses that will be offered in different departments, for example, in the medical schools and engineering departments. In addition, the Alliance has a training component administered through the F32 and F33 mechanisms. An attempt also is being made to connect groups and investigators in schools strong in physics and engineering with some components of the CCNEs. Dr. Barker added that extensive research was conducted before the nanotechnology plan was written to identify the areas with clinical training needs. The decision was made to focus much of the NCI effort on the clinicians who are at the bedside today as they will be the implementers for the next several years. The young people coming along already will have had training in the technology.

Dr. Freedman asked where and by whom the clinical trials, particularly the exploratory trials, will be reviewed, considering that much of the science is being developed within academic institutions where there may be a limited number of individuals with expertise in this area. Dr. Barker replied that the NCI and the NIH have been working on the policy implications, not just around this kind of science, but especially around issues such as privacy and control and stewardship of tissues. For the nanotechnology program, the NCI is working closely with the FDA through the Interagency Oncology Task Force. One group is focusing on nanotechnology to deal with issues such as risk, environmental exposure, and toxicity, and the NCL has been pivotal in that regard. In addition, the issues surrounding early-stage clinical trials are being addressed in the implementation of Clinical Trials Working Group (CTWG) recommendations.

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

Dr. Elias Zerhouni, Director, NIH, explained that he would be presenting a strategic perspective about the NIH, in general, and about the context in which the NIH is evolving, how this may be affecting the NCI, and the adaptive strategies being considered and put in place by himself and the Institute Directors. He cited the need to address the dynamics of what is happening in terms of the NIH budget and NIH research, for example, the ability to enter emerging fields of science, as well as the issues being grappled with in the community in general. He briefly reviewed forces driving the "perfect storm" that the NIH budget is facing in 2006, including the federal and trade deficits, defense and homeland security needs, across-the-board budget reductions to fund recovery efforts after Hurricane Katrina, and the need to prepare for pandemic flu. Two generic effects relating to the NIH's policy-making environment are the post-doubling effect and related expectations of policymakers for accountability, and the fact that there is a renewed focus on the physical sciences because of the issue of national competitiveness. In addition, biomedical research inflation (3-5 percent) is higher than general inflation. Dr. Zerhouni noted that these forces taken together explain the anxiety of scientists, a veritable "NIH-at-the-crossroads" syndrome.

To put the current situation in perspective, Dr. Zerhouni reminded members that extreme cycles like these are part of the history of the NIH; for example, the same syndrome occurred in 1982. Understanding the fundamentals is a key requisite to having an informed debate on adaptive strategies to be used by the NIH going forward. He noted that multiple meetings of NIH Directors and staff have been held since 2004 to address those fundamentals. He listed and discussed the impact of the three fundamental drivers of the current syndrome: large capacity building throughout U.S. research institutions and an increase in the number of new faculty, appropriations below inflation after 2003, and

the budget-cycling phenomenon. The increased investment in infrastructure was a response by the U.S. deans of research in 1999 to the emergence of new areas of science and the profound need for more research for many diseases. Specifically, Dr. Zerhouni cited data from the American Association of Medical Colleges (AAMC) survey of research facility investments, which show that the period from 1997 to 2007 saw the largest investment in biomedical research capacity (more than $15 B) for any short period of time in history. This investment has put the United States in a position of worldwide leadership in terms of the ability to compete in health care, which promises to be the premier economic activity in the world for the next 30 or more years. Dr. Zerhouni expressed the view that the life sciences will be defining in terms of science and technology.

Dr. Zerhouni noted that this increased capacity building translates into interesting phenomena. The increased competitiveness of grants and difficulties of the NIH can be seen by looking at the most sensitive parameter—the success rate of grants funded per grant application, which hovered at 30 to 31 percent during the budget-doubling period and began to decrease after 2003. In terms of capacity building, however, what occurred was a dramatic increase in the number of applications received by the NIH—from 24,000 in 1999 to 43,000 in 2005 and a projected 49,000 in 2007, twice as many as before the doubling. An analysis of this increase shows that the curve depicting the number of applications received was relatively linear until 2002 when it accelerated by a rate of 2.5 times. There was a lag time between the doubling and the demand for grants. Further analysis in 2002-2003 to understand these dynamics revealed that the total growth in number of applications that the NIH received for the 5 years of the doubling was about 8,303. In 2 years following the doubling, the incremental growth has been 8,359 per year. Dr. Zerhouni explained that these numbers do not mean that the NIH is receiving more applications per scientist. It indicates, rather, that an effective system has been built by which new scientists are applying to the NIH for new research. The number of new scientists applying every year to the NIH grew by about 5,300 between 1999 and 2003; in 2005, the number was 5,208, a doubling of the scientific demand for grants and research in the 2 years following the doubling. Dr. Zerhouni suggested that this is good news, indicating that institutions and the scientific world have responded to the rising public health demands and the need for new knowledge.

To dispel the notion that the loss of purchasing power is the main reason for the budget stress in 2006, Dr. Zerhouni stated that the demand/supply imbalance brought about by the post-doubling “boom” in applications accounts for 80 percent of the increased competitiveness and the drop in success rates. The increased cost of grants, coupled with inflation effects, accounts for 20 percent of the stress—70 percent more scientists are applying for twice as many grants than in 1999, and grants are 40 percent more expensive. Projections for FY 2007 indicate that NIH funding will experience a 7.3 percent loss in purchasing power if the budget stays as proposed; the loss in FY 2006 is about 1.5 to 2 percent. Dr. Zerhouni explained the budget cycling phenomenon, noting that it is another reason for the cycle downturn being seen in FY 2006. Because grants are funded for 4 to 5 years, dollars to fund new research come from the ending of grants started 4 to 5 years previously and added to budget increases in the NIH appropriations. Inasmuch as there was no increase in FY 2006, the flexibility for that budget has decreased significantly. Dr. Zerhouni noted that the NIH will be able to increase the competing grant pool by 3 percent in FY 2007, even with a flat budget, because of the recirculating dollars from an earlier period of time.

Next, Dr. Zerhouni responded to the question on everyone’s mind as to what the chances are of being funded. To address common misconceptions, he reminded members that the payline is not the funding cut-off line. It is the line where everybody gets funded, but there is always a distribution beyond that. So the success rate per application is always higher than the payline. Furthermore, the success rate per application understates the likelihood of any scientist being funded. Data over the past 10 years at the NIH indicate that the success rate per application is almost always 5 percent below the success rate per

applicant. For example, the success rate per application in FY 2005 was 22.3 percent but 27.6 percent for applicants. This year, the success rates are estimated to be 20 percent for applications and 25 percent for applicants. He expressed the view that the steady state should be more in the upper 20s, but that the situation is not as dire as perceived in the community. He emphasized the need for understanding the concern at the NIH for maintaining a viable enterprise on the basis of natural competitiveness and the prospects for advances in cancer research.

Dr. Zerhouni presented data to address three common misperceptions: (1) that the NIH is overemphasizing applied research; (2) that the NIH is shifting towards solicited research with too many RFAs; and (3) that the NIH Roadmap is shifting major funds away from the grant pool. In the first instance, data show that, in 1998, 53.9 percent of the budget was devoted to basic science and 40.5 percent went to applied research. Today, the percentages are 55.8 percent for basic and 41 percent for applied sciences. Dr. Zerhouni noted that the temporary decease in basic science funding in 2003 was due to the $1.6 B budget to accommodate for the need for post-9/11 biodefense. The historical balance resumed in 2004 and 2005 because all of the construction was accounted for in 2003, and the biodefense money reverted to the grant pool in 2004 and 2005. In regard to the perceived shift toward solicited research, Dr. Zerhouni presented NIH data that show 91 percent of the grants were awarded for unsolicited research in 1994 and 93 percent in 2005. By contrast, RFA-generated awards constituted 9 percent of the NIH budget in 1994 and 7 percent in 2005. He declared that every Institute since 2003 has been cautious about launching large trials or investments except in the areas of emerging needs such as nanotechnology. In addressing the misconception that the NIH Roadmap shifts major funds from the grant pool, Dr. Zerhouni reminded members, first of all, that the Roadmap was developed in consultation with hundreds of scientists at the urging of the Institute of Medicine in a report relating to congressional concern about synergy across the Institutes. He noted, second, that the Roadmap accounts for 0.8 percent of the NIH budget and that the Roadmap is not a single initiative but more than 345 individual awards in FY 2005 to 133 institutions in 33 states (basic, 40 percent; translational, 40 percent; high risk, 20 percent). The grants are focused on individual scientists conducting leading-edge and enabling research and incubating new ideas; the Pioneer Award is an example of this. Dr. Zerhouni proposed that having a small fund going to all of the Institutes to try emerging areas of science (such as molecular libraries or nanomedicine) is an important tool to generate increased synergy, inasmuch as science is converging across fields now.

To address concern in the cancer community that the Roadmap takes resources away from cancer research, Dr. Zerhouni informed members that an analysis of the issue by both the NIH and the NCI shows that NCI grantees have consistently received more than the NCI contributed to the Roadmap, and this does not include cancer research performed by non-NCI grantees. In FY 2005, NCI grantees received $42.1 M (of the Roadmap total of $240 M) in awards and the NCI investment in Roadmap was $30.5 M. Dr. Zerhouni pointed out that most of the NCI-grantee awards were in the basic science component of the Roadmap in areas such as computational biology of cancer, high-throughput biology, and protein membrane structures.

Next, Dr. Zerhouni discussed future directions for the NIH. He enumerated fundamental principles behind the strategies that will need to be implemented to weather the current situation: (1) protect core values and generate new knowledge, (2) protect the future, (3) manage the key drivers, (4) communicate proactively, and (5) promote NIH's vision for the future. Dr. Zerhouni elaborated on strategies to be implemented based on these principles. The NIH will work to accelerate, at the fastest pace possible, discovery and the generation of new knowledge in the diseases of concern. Because the future resides in the new young investigators, who are most vulnerable members of the scientific capital of the country, the NIH has launched the Pathway to Independence Program and has asked every Institute and Center to consider strategies to make sure that a generation of new scientists is not lost. The NIH will

strive to manage the key reason for the crisis, which is the imbalance in demand and supply. Because investigator-initiated research is the area where the demand has increased the most, the NIH will focus on addressing the demand/supply equation as the budget is recycling from grants awarded in 2001-2003. Dr. Zerhouni reminded members that communities that manage crises well have good information, good leadership that analyzes the situation, and unified communication of the issues and terms of reference for the debate that needs to happen. Proactive communication about the NIH, therefore, means demonstrating the value of NIH's investment, doubled or not, and the need for sustainability and understanding the consequences over the long run of not sustaining the investment. Finally, the vision for the future should support continued excitement about where the NIH is going.

Dr. Zerhouni related that NIH leadership testimony at recent congressional hearings promoted the return on investment and the vision for the future. Cancer and heart disease were used as two examples of the progress that has been made. For cancer, annual cancer deaths in the United States have fallen for the first time in recorded history (there are now 10 million survivors); improved effectiveness of early detection and screening has occurred; and paradigm-shifting research has been successful in developing targeted, minimally invasive treatments for cancer and improving prospects for personalized cancer treatment. Dr. Zerhouni acknowledged that challenges remain but the progress is real, and he pointed out that the investment per U.S. citizen has been $8.60 per year or a total of $260 over the 30 years of the investment in cancer. Similar data in heart disease, prevention of blindness, arthritis, and musculoskeletal disease also attest to the value of the NIH investment.

Dr. Zerhouni spoke further on the need to stay true to the NIH mission, which is as a knowledge-generation engine. He described the NIH as a pyramid of investments with about 60 percent in basic research and technology development, 25 percent in translational research, and 15 percent in clinical applications. The pyramid is inverted in the private sector where translational and clinical research are predominant. Together, the two pyramids form a balanced portfolio for the United States, and the balance should be maintained, he stated. Dr. Zerhouni concluded that the United States is threatened in terms of its fundamental competitiveness by the cost of health care, and the challenge can never be overcome if the practice of medicine and health is frozen in today's mold. At the same time, life sciences present the greatest opportunity. He stated that the future paradigm for the NIH is to transform medicine from curative to preemptive and that cancer research is a good example of that—more predictive, more personalized, more preemptive, but also more participatory. He emphasized that participation by patients and communities will be critical to early detection, early screening, early intervention, and preemption of disease.

Dr. Zerhouni solicited help from NCAB members in the areas of proactive communication and promoting NIH's vision for the future. The message to be communicated is: There are fundamental drivers that occur historically at the NIH because of the partnership between private sector and federal investment. As the private sector investment rises, demand increases and needs to be matched with federal investment. That explains the prevailing sense that, despite the budget doubling, competition for research grants has increased. This is fundamentally good for the country and needs to be sustained. The underlying dynamics need to be understood and adaptive strategies developed, but, more importantly, continued support is needed for the vision that the NIH has for itself of transforming medicine and health through discovery.

Questions and Answers

Ms. Giusti observed that a person's likelihood of getting cancer and the fact that the investment is only $8.60 per person per year should be communicated more clearly. From a patient's perspective, she expressed gratitude for the budget doubling, the infrastructure that was built, and the improved care

received in the Cancer Centers but questioned whether all of it translates to treatment and whether the new therapies are extending lives. She enumerated some of the obstacles to translation that remain. Dr. Zerhouni briefly described the NIH's efforts to address the roadblocks that exist, including meeting with industry and the FDA to analyze what the roadblocks are and promoting the idea of public-private partnership. He called attention to a new program for academic institutions called Clinical, Translational and Science Awards to promote an institutional focus on the issue of translation and to develop a new generation of translational scientists who understand the complexity of the science as it is known today.

Dr. Diana Lopez, Professor, Department of Microbiology and Immunology, University of Miami Miller School of Medicine, expressed concern that scientists in the 40 to 50 age range appear to be contemplating career changes because of the difficulty in obtaining funding. The result would be a reduced number of mentors for the training of future generations. Dr. Lopez concurred with the need to communicate Dr. Zerhouni's message. Dr. Zerhouni expressed confidence both that the NIH would get to the facts and develop a unified strategy and that the patient, stakeholder, and scientific communities will respond to the message. Dr. Niederhuber pointed out that the nature and demands of science are changing as well as the demands of technology around tomorrow's science. He expressed the view, therefore, that a change in the culture in academic universities is needed to move more toward teams and to rewarding that type of participation. Dr. Zerhouni agreed that there is a need to have a full portfolio of attempts—both individual and team research—and that the key thing is to remove barriers to innovation and risk taking, as well as artificial barriers to science to enable the free association of bright scientists who have new ideas about how to conduct science. Dr. Armitage pointed out that leadership also will be needed to change the way that medical schools promote their staff and the basis for making awards such as those reported earlier.

Dr. Zerhouni closed by recognizing the contributions made by volunteers to the NIH and thanking them. About 31,000 scientists, members of the public, and advocates come to the NIH annually to provide peer review, advisory services, counsel, and review of the intramural program in so many capacities as to constitute a body larger than any other consulting firm in the world today. He also recognized the work and contributions of the staff and scientists at the NCI, which he characterized as the crown jewel of the NIH.

X. NCI/CMS/FDA COLLABORATION—DR. ANNA BARKER

Dr. Barker presented information about a unique relationship between the NCI, the FDA, and the Centers for Medicare and Medicaid Services (CMS) to expedite the development of cancer therapies through the Oncology Biomarker Qualification Initiative (OBQI). She mentioned that an issue of *Science* (May 26, 2006) discussed biomarkers and how they will play into 21st century personalized cancer care, quoting from an article in the issue by Drs. William S. Dalton and Steve H. Friend: "The emerging use of cancer biomarkers may herald an era in which physicians no longer make treatment choices that are based on population-based statistics but rather on the specific characteristics of individual patients and their tumor."

Dr. Barker described the beginnings of this collaboration. In 2003, the Interagency Oncology Task Force (IOTF) was established between the NCI and the FDA to enhance the efficiency of clinical research and the scientific evaluation of new cancer treatments. The IOTF focused on several areas, such as establishing joint training and fellowships. Dr. Barker noted that there now are 15 fellows in this program whose work range from medical oncology to prevention, and they spend their time at the FDA actually in regulatory review. In addition, the task force has worked to discover and develop biomarkers for clinical benefit, as well as, through the use of caBIG™, standardize bioinformatics platforms for clinical trials and all associated electronic filings. The IOTF has tried to address specific regulatory

barriers that impede the development of cancer drugs. In addition to the OBQI, the task force supports initiatives involving many other issues across the drug development and regulatory processes, such as the exploratory investigative new drugs (IND), which FDA released guidance on late last year, advanced technologies and molecular diagnostics, and new common bioinformatics platforms. The OBQI supports the development of the FDA's Critical Path Initiative along with the science that the NCI is developing. The FDA's Critical Path targets five areas: (1) developing biomarkers in new disease models; (2) streamlining clinical trials; (3) applying bioinformatics, which is an important focus of the IOTF and the OBQI; and (4) enabling 21st century manufacturing; and (5) addressing urgent public health needs. Dr. Barker said that she would devote much of the rest of her talk to the OBQI's work in terms of developing biomarkers in new disease models.

Dr. Barker took a moment to describe this year's ASCO convention, at which she witnessed a real movement into targeted agents. She expressed her amazement at the number of quasi-breakthrough drugs that were discussed across the ASCO program; in past years, there had been one big announcement about one drug, such as Gleevec® or Herceptin®. An article in *The New York Times* about the convention pointed out that there was a notable presence of pharmaceutical companies, who were engaged in creating the second generation of many of these agents as well as creating their own agents. In addition, the article reported that the entire drug market today for cancer therapeutics is about $25 billion and is estimated to double within 10 years to $50 billion. Dr. Barker pointed out that, for its company of origin, Gleevec® brought in about $2.2 billion last year, breaking the billion-dollar barrier and turning out to be an extremely profitable drug.

All areas for biomarker development will need to be enabled, including new target discovery, which is occurring mostly in the private sector. Drug development is benefiting from biomarkers, and Dr. Jerry Collins, NCI's Developmental Therapeutics Program, is working directly with FDA in the area of pharmacogenomics, particularly with markers of toxicity and metabolism. One of the areas that is tied to development is early detection, or the prescription-diagnosis model. In addition, identifying the molecular basis of disease phenotypes, assessing disease aggressiveness, making a rational choice of treatments and assessing the effectiveness of treatments are all important. Finally, there is a great need for prevention markers.

There are a number of technical, regulatory, economic, and structural gaps in the current system that hinder the rapid development and adoption of biomarkers in clinical care. One is that standards are needed to evaluate technologies and compare experimental results. Some of the regulatory barriers—such as the need for qualified biomarkers to use in FDA guidance for cancer drug development—are solvable problems. However, this is not a cheap endeavor. From an economical perspective, innovators are reluctant to conduct biomarker trials without evidence of widespread clinical application; the CMS needs evidence of clinical utility to inform reimbursement decisions, and the private payers obviously will be difficult in this regard. Some of the structural issues relate to the system itself. Biomarker-based studies require a multidisciplinary team that is knowledgeable about the advanced technology, biology, and engineering in terms of the device that is being used to measure the biomarker. There is a very high need for bioinformatics. The FDA/NCI/CMS partnership is a coordinated effort to bridge all of these barriers.

A tri-partite memorandum of understanding (MOU) for this was signed in early January 2006. The OBQI is a pilot project for a larger NIH biomarker initiative and represents the pilot for this public-private partnership. Dr. Barker named top scientists who have been working on this project, several of whom were present, including Drs. Gary Kelloff, Janet Woodcock (FDA), and Dan Sullivan.

The three collaborating organizations have developed goals for the OBQI to coordinate. The NCI, for example, expects the OBQI to develop biomarker technologies and validation protocols to

improve detection, diagnosis, treatment, and prevention of cancer. The FDA has requested the OBQI to develop guidance for the use of biomarkers to facilitate cancer drug development. Finally, the CMS would like the initiative to make informed decisions about reimbursement of new or existing treatment regimens based on biomarker-guided knowledge. The OBQI will validate particular biomarkers to: (1) evaluate new, promising technologies in a manner that will facilitate and accelerate clinical trials; (2) reduce the time and resources spent during the drug development process; (3) improve the linkage between drug regulatory review and drug coverage; and (4) increase the safety and improve the efficacy of drug choices for cancer patients.

Four focus areas have been developed for the OBQI. Cancer imaging is at the top of the list because the FDA said that there are enormous amounts of data on imaging in various cancers, which hold great promise for biomarkers. Another focus area is that of molecular assays and targeted therapies, which are aimed to develop scientific bases for diagnostic assays to enable personalized treatments. Dr. Barker stated that the NCI is working in a public-private partnership with the FDA and the C Path organization to begin to standardize these platforms across many companies. In addition, clinical trials and data mining (that is, pooling to share data and learning between trials) are two other focus areas.

Dr. Barker next turned to the role of imaging-based biomarkers. She shared a quotation from Dr. Ralph Weissleider, University of Pennsylvania: "Imaging-based biomarkers can be used in all phases of the cancer drug development process, from target discovery and validation to the pivotal clinical trials that precede drug approval." (*Science* May 26, 2006). Imaging used in this way could lead to much smaller clinical trials, earlier approval or rejection decisions on compounds, accelerated regulatory review, a shorter time to get to patients, and surrogate markers of efficacy.

The OBQI has looked at fluorodeoxyglucose (FDG) PET, which shows promise as one of the older young technologies. It exploits a fairly simple metabolic activity in cells, targeting the tumor cell's reliance on glucose and the glycolytic metabolism of imaging cancers. Scientists can analyze it visually, semi-quantitatively, and also increasingly quantitatively. Moreover, it has been reviewed extensively and approved by the FDA for use in the diagnosis, staging, and restaging of a number of cancer types, and can impact the clinical management of disease. In a number of clinical settings (e.g., NSCLC, esophageal cancer, and lymphoma), FDG-PET can provide an early measure of response to treatment with approved therapies. With a few additional studies, FDG-PET could facilitate drug development and patient care by resulting in shorter Phase II trials, accelerated approval in Phase III, with a follow-on showing clinical benefit, and better patient care by stopping ineffective therapies. For further information, Dr. Barker referred the Board to the article "Progress and promise of FDG-PET imaging for cancer patient management and oncologic drug development" (Kelloff GJ, et al. *Clin Cancer Res* Apr 15, 2005;11(8):2785-808).

Dr. Barker reiterated that the OBQI serves as a pilot program for the larger NIH initiative, and multiple partners will be involved, in addition to the three federal partners. The Foundation for the NIH will be bringing in private partners to pay for these trials, and will help with various activities in the trials, including: finalizing the clinical question, collaborating with community experts to develop and finalize the protocol, seeking partners, and being involved with trial performance.

There are two initial projects focused on imaging-based biomarkers: (1) FDG-PET imaging in non-Hodgkin's lymphoma to predict tumor response to treatment; and (2) FDG-PET imaging in NSCLC to predict tumor response to treatment. Both projects incorporate a new approach, involving multiple clinical trial sites that all follow the same protocol and share data in real time via caBIG™. The project addressing non-Hodgkin's lymphoma is being led by Dr. Dan Sullivan and his colleagues. This cancer was chosen because there is a history of successful clinical management, effective drugs, existing clinical

FDG-PET data for diagnosis and staging, and established treatment-response criteria that can be refined by FDG-PET. The objectives are to refine the criteria with FDG-PET imaging and establish predictive values after two cycles of chemotherapy. Approximately 20 sites will be selected and will include Comprehensive Cancer Centers. About 400 patients will undergo standard chemotherapy treatment, with imaging occurring at baseline and after Cycles 2 and 6 of chemotherapy. The NSCLC project aims to determine if FDG-PET scans can be used as a surrogate marker of efficacy in lung cancer treatment. It is expected that 15 sites will be selected, including NCI's cancer centers, and that approximately 200 patients will be included in the trials. Standard platinum-based therapy for lung cancer will be utilized, with three cycles of therapy.

The next steps for the OBQI are to finalize the structure for these public-private partnerships to fund biomarker trials. This likely will be announced in summer 2006. In addition, teams and sites will be selected for the first two trials, with potential sites under consideration and hopefully selected and funded in fall 2006. A third step is to determine the next OBQI trials; an expert group will identify next trials in fall 2006 as well.

Dr. Barker concluded with a picture that represented the idea that the development of personalized cancer care will involve qualifying biomarkers. She pointed out that the term "qualification" is distinct from validation. How one might validate relative to a question around biochemistry or the biochemical activity of a cell, for instance, is different than qualifying agents for regulatory activity or for CMS reimbursement. Dr. Barker reiterated the importance of the initiative and the NCI's role in it. Non-Hodgkin's lymphoma and NSCLC are diseases that sit two ends of the spectrum in terms of a public health problem. Although scientists are far along in terms of understanding both the molecular pathways of this disease and its treatment, neither have defined biomarkers to allow trials from which to increase the number of what Intel co-founder Andy Grove terms "information turns." "Information turns" expedite the flow of knowledge to expedite the process of returning to the bedside and redesigning. On behalf of herself and Dr. Kelloff, she thanked their colleagues and partners on OBQI, Drs. Woodcock and Peter Bach, CMS.

Questions and Answers

Dr. deKernion asked how PET might be used to help predict a response. Dr. Kelloff replied that one of the OBQI activities is to take the lead data that suggest that one round of chemotherapy can reveal a trend that then is predictive of survival. The data, however, have been analyzed retrospectively in trials that are ongoing; no perspective trials have been purposefully planned looking forward to having prospectively defined cut points and quantitative imaging brought to it to ascertain how good the predictive value is. It appears that FDG-PET in lung cancer can help to provide the evidence-based and clinical data that both the CMS and the FDA require. In oncology and drug development, earlier development of data brings many implications for therapy management. The most important part of this is the public-private partnership and the range of players involved: federal agencies, the pharmaceutical industry, the scanner and device industries, and the advocacy community. It is an opportunity to leverage NCI's resources and allow everybody at the table in the partnership to voice their opinion in a way that is constructive.

Dr. Armitage expressed his approval for the project, noting that it will move the NCI and industry more quickly to where they need to be as well as keep the PET technology from being abandoned because people become frustrated by its use. He noted that the interesting problem will relate to cost, because if this works, the cost savings will halt or diminish the use of other imagery tools or perhaps other tests.

Dr. Runowicz wondered whether the NCI will collect a biorepository for future markers that then can be correlated with what has been obtained through the PET. Dr. Barker responded that the NCI is selecting biorepositories now for several activities, most prominently for the Cancer Genome Atlas. Regarding imaging biomarkers, most of the work probably will need to be accomplished prospectively. Dr. Barker noted that, to conduct these trials, first-class biorepositories will be needed. Ms. Giusti asked about trials planned in addition to non-Hodgkin's lymphoma and NSCLC, and whether standard chemotherapy or other agents will be used. Dr. Kelloff answered that trials addressing other cancers will be considered, provided that standardized imaging technologies are available. A known chemotherapy likely would be used because of the wealth of experience and knowledge about the survival and progression curves. Dr. Barker added that a list of approximately 15 biomarkers does exist to help with these decisions. Dr. Peter Kirchner, Senior Scientist, Department of Energy, wondered whether, in addition to a biorepository, an imaging database would be created, noting that it would be a valuable resource for mining.

XI. UPDATE: CANCER INTERVENTION AND SURVEILLANCE MODELING NETWORK—DR. ROBERT CROYLE

Dr. Kerner introduced the subject and speakers for the session on CISNET. He filled in for Dr. Robert Croyle, Director, DCCPS, who was representing Dr. Niederhuber at an NIH-wide consensus conference on tobacco use, prevention, cessation, and control. The CISNET can serve as a model for how science can inform policy decisions and how team science can work well collectively and still reward individual innovation. Dr. Kerner encouraged to Board to provide suggestions on how to use the CISNET as a resource to help inform the National Cancer Program and its leadership through the context of mathematical modeling.

Overview—Dr. Eric J. Feuer

Dr. Eric J. Feuer, CISNET Program Director and Chief of the Statistical Research and Application Branch in NCI's Surveillance Research Program, expressed his appreciation for the opportunity to speak about CISNET. He pointed out that the meeting materials include lists of members of the CISNET consortium and grantees, a list of CISNET publications and abstracts, and a copy of "Effect of screening and adjuvant therapy on mortality from breast cancer" (Berry DA, et al. *NEJM* 2005;353(17):1784-92). CISNET is an NCI-sponsored consortium of modelers, set up as a cooperative agreement to foster collaboration between NCI staff and grantees. It focuses on modeling the impact of cancer control interventions—screening, treatment, and primary prevention—on current and future trends, as well as a closely related area, optimal cancer control planning. It originally was funded in two phased rounds in fiscal year (FY) 2000 and 2002 and refunded in FY 2005. There are 15 grants funded in four cancer sites (breast, prostate, colorectal, and lung) and five affiliate members, who are funded through other mechanisms at the NIH but who joined the CISNET collaboration. The CISNET Web Site, http://cisnet.cancer.gov, provides additional information.

CISNET provides tools and models for the evaluation of the delivery of interventions at the population level. In the original issuance, the network began with basic mathematical and statistical relationships necessary to develop multi-cohort population models; it later shifted to the development of data sources, realistic scenarios to evaluate past population impact of interventions, and the projection of future impact. In the re-issuance, development continues, but the emphasis is on delivery, including the synthesis of relevant scenarios for informing policy decisions and cancer control planning and implementation. Delivery involves using these models to translate the state of the science to assist informed decisionmaking. The questions addressed range from narrow, scientifically focused problems to national policy issues.

CISNET differs from other modeling efforts in that it offers a comparative modeling approach. Dr. Feuer shared results from four independently published studies on the cost effectiveness of spiral CT screening that varied from a low of $2,500 up to $154,000 per quality adjusted life year saved. The studies used individualized criteria—for instance, differences in the target population, screening frequency, stage shift, assumptions about lead time and overdiagnosis, and sensitivity—which prevents comparison among them. CISNET, however, employs an approach that defines specified questions that are tackled jointly. Certain population-level inputs, such as the dissemination and patterns of mammography or prostate-specific antigen (PSA) testing in the United States, or smoking patterns in the United States, are developed jointly and shared. These comparative analyses provide a context for future individual modeling efforts.

Dr. Feuer next described five unique scientific opportunities for CISNET. (1) CISNET is responding to challenges associated with the increasing pace of technology. For example, in 2002 *The New York Times* published an article, "Prostate Cancer: Death Rate Shows a Small Drop. But Is It Treatment or Testing?" (April 9, 2002). Subsequently, members of the CISNET prostate group have run two models of prostate cancer screening, which independently suggested that PSA screening can account for about 50 percent, but not all of the mortality decline is attributable to screening under the stage shift assumption. Modeling treatment has involved the efficacy (from randomized control trials [RCTs]) and the dissemination of treatments, and Dr. Feuer described the analyses of hormone ablation therapy adjuvant to radiotherapy using the CISNET approach. (2) The models can be used to develop more focused discussions in areas of controversy. For instance, regarding the debates over the natural history of lung cancer and spiral CT screening, modeling has allowed researchers to examine how the growing body of evidence for spiral CT screening enhances the understanding of the natural progression of lung cancer. Each screening test provides a glimpse into the arena of unknown natural history. Moreover, modeling allows the extrapolation of the conditions of a trial to different scenarios. Discussions to develop collaborations with the National Lung Screening Trial and the Early Lung Cancer Action Project are ongoing, with the hope of using modeling to develop a platform for focused discussions between these two groups. (3) CISNET can provide estimates of quantities that will never be derived from RCTs, which particularly affects smoking. Some of the common inputs are U.S. smoking histories and life tables for all causes other than lung cancer by smoking history. Individually modeled inputs include the natural history of disease, including lung cancer development, growth rates, and metastatic spread. The CISNET models yield comparative results on predictive incidence and mortality by smoking status. (4) Completed RCT evidence can be translated to the population setting. This has been seen in the impact of adjuvant therapy and mammography on U.S. breast cancer mortality; Dr. Don Berry's presentation, below, provides further details about this. (5) CISNET is working to communicate modeling results effectively to cancer control planners and policymakers; Dr. Zauber's presentation summarizing oingoing work on a cancer projections Web site for colorectal cancer illustrates this effort.

Breast Cancer Initiative—Dr. Donald Berry

Dr. Donald Berry, Chair, Biostatistics and Applied Mathematics Department, MD Anderson Cancer Center, shared details about a joint analysis of a breast cancer base case. The aim was to assess the impact of adjuvant hormonal therapy, chemotherapy, and screening mammography on breast cancer mortality in the United States from 1975 to 2000. Between 1990 and 2000, mortality due to breast cancer dropped substantially by 24 percent. Extrapolating to the future, if the use of interventions remain at the current levels, then the age-adjusted breast cancer mortality rate will actually start to increase. The number of breast cancer survivors, however, will continue to decrease. In addition, there are substantial innovations in science, screening, and adjuvant therapy that appear promising.

Population models involve common inputs, such as background trends, screening behavior, and diffusion of new treatments, among others that CISNET feeds into seven breast cancer models—which is more models addressing a single question than any of the other disease sites—to analyze breast cancer incidence and mortality. Dr. Berry noted that the CDC and the NCI made their data sources available to CISNET for these models. To illustrate the type of information used, he shared a chart of mammography screening over time for women ages 40-79 that indicated that screening increased between 1985 and 2000. An additional graph displayed the use of adjuvant therapy, focusing on the benefits of polychemotherapy, tamoxifen, or both. It became clear in 1988 that ER-negative patients did not benefit from the use of tamoxifen.

Dr. Berry next described modeling results, beginning with one of the seven models that examined the mortality rate per 100,000 women ages 40 to 79 under scenarios involving screening, treatment, or both or neither of them. This model projected that about one-half of the drop in the mortality rate was attributable to screening and the other half was attributable to treatment. Dr. Berry also presented a summary table of the seven models showing percent reductions in breast cancer mortality. Five conclusions were developed from these studies using these models: (1) screening lowers breast cancer mortality; (2) the benefit from population treatment is similar to clinical trials; (3) there is little evidence for synergy; (4) there are some model differences; and (5) there is overall robustness across models in that screening and therapy both play a role. An editorial in *The New York Times* commented that, "What seems most important is that each team found at least some benefit from mammograms. The likelihood that they are beneficial seems a lot more solid today than it did 4 years ago, although the size of the benefit remains in dispute."

Major CISNET publications include "Effect of screening and adjuvant therapy on mortality from breast cancer" (Berry DA, et al. *NEJM* 2005(17);353:1784-92). In addition, a forthcoming *JNCI Monograph* (summer 2006) is dedicated to breast cancer CISNET that describes in great detail the inputs, data sources, descriptions of the models, and comparisons of the various assumptions, intermediate outcomes, and mortality.

Future work for CISNET involves individual groups modeling risk factors and optimal screening to determine the impact of the individual therapy focusing on high-risk populations, disparities, socioeconomic status, and race. Some of the groups are participating in Healthy People 2010 (HP2010). The second base case is modeling impact of the new therapies on breast cancer mortality, primarily from an individualized perspective. Therapies will focus on new targeted treatments—such as Herceptin®, Lapatinib, Bevacizumab, and aromatase inhibitors—and individualized therapies, including Adjuvant!Online, Oncotype Dx, and chemotherapy benefit by ER/HERs. Chemoprevention also will continue to be studied, specifically involving the agents tamoxifen and raloxifene; it is unknown how raloxifene, which clearly prevents or delays ER positive tumors, will be used in the Study of Tamoxifen and Raloxifene (STAR) trial.

Dr. Berry described results and benefits of breast cancer trials involving various agents. One focused on trastuzumab (Herceptin®) in HER2 positive adjuvant breast cancer. In another instance, a paper published in April showed enormous successes in node-positive breast cancer therapy during the past 15 years; it reported on three trials designed by the U.S. Breast Intergroup that together revealed benefits for ER negative patients, but noted that there was little benefit for chemotherapy in ER positive patients treated with tamoxifen. A third study compared the benefits of paclitaxel on disease-free and overall survival based on HER2 and ER statuses.

Colorectal Cancer Initiative—Dr. Ann Zauber

Dr. Ann Zauber, Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering, presented information about CISNET's colorectal cancer program, focusing on micro-simulation modeling. She discussed an example of how much current interventions can reduce colorectal cancer mortality in the United States. These findings can help determine the best short- and long-term choices for cancer control interventions. Dr. Zauber serves as the biostatistician for the National Polyp Study, which is an RCT to assess what should be the colonoscopy surveillance intervals for patients who have adenomas. Results from this study as well as others have been used to develop a model for the natural history to predict adenomas and colorectal cancer outcomes. The micro-stimulation model being used is called Micro-simulation for Cancer (MISCAN).

CISNET modeling has been used to inform health policy. One example is that CISNET was tasked with helping to determine what the CMS reimbursement should be for a new fecal occult blood test (FOBT), called the immunochemical fecal occult blood test. (FIT) Previously, screening with guaiac fecal occult blood tests had shown in RCTs that colorectal cancer mortality could be reduced 15 to 33 percent. CISNET focused on the reimbursement relative to the increase in effectiveness for the new FIT relative to the older guaiac FOBT and suggested that the reimbursement fee be set at $22.22 per test. Other examples of CISNET's modeling work include: impact of screening, treatment, and risk factor effects on CRC incidence and mortality from 1975 to 2000; clinical processes that affect the survivorship and the quality of care for colorectal cancer for the Cancer Care Quality Measurement Project (Canqual); customizing colonoscopy screening by race and the age to begin screening; and the impact of missing diminutive adenomas with virtual colonoscopy.

A micro-simulation modeling for colorectal cancer involves adenomas (i.e., the precursor lesions for colorectal cancer), the adenoma carcinoma sequence, and finally clinical colorectal cancer. Dr. Zauber displayed first a chart showing how modeling takes this biological process and models it mathematically, followed by a chart that illustrated interventions on colorectal cancer. In addition to the natural history of colon cancer—that some adenomas grow, have the potential to develop into preclinical and clinical cancer, and cause death—the MISCAN Model assumes that some of the adenomas that develop have the potential for growing but do not have the potential to keep progressing; these are adenomas with very low malignant potential and are referred to as nonprogressive adenomas. In addition, some of the non-progressive adenomas can regress. This process could be repeated, and a person could end up with no adenomas, or have up to four or more, located at multiple sites. The CISNET modeling accounts for these and other possibilities as well as multiple risk factors. Other causes of death, such as cardiovascular diseases, are being considered in the modeling for colorectal cancer.

Dr. Zauber next addressed the issues of the best short- and long-term interventions for colorectal cancer. Healthy People 2010 have set mortality goals for cancer. Between 2003 and 2010, to reach the Healthy People 2010 mortality goals, mortality would have to drop by 12 percent for female breast cancer, 17 percent for lung cancer, and 27 percent for colorectal cancer; colorectal cancer is the second leading cause of cancer death in the United States. Goals for the Healthy People 2010 agenda are the same for all race and sex groups; to achieve the goal, the decrease in colon cancer mortality needed for white men is 38 percent; black men, 57 percent; for white women, 10 percent; and black women, 39 percent. Risk factor trends, screening behavior, and the diffusion of new treatments—that is, "upstream"—are considered in the population simulation model to predict colorectal cancer incidence and mortality—that is, the "downstream" goal. Dr. Zauber explained this through an example of colorectal cancer in white men, noting that data also are available for black men, as well as white and black females. In 2003, the rate was 22.4 per 100,000, on a downward trend since 1973. This decline is attributable predominately to past screening and somewhat to chemotherapy. To continue the reduction, upstream

factors are modeled. Specific risk factors are considered, such as smoking, obesity, physical activity, multivitamin use, red meat, aspirin, food and vegetable consumption, and hormone replacement therapy. Obesity, for example, which is increasing markedly in the United States from 8 percent of the population in 1970 to 30 percent in 2005, was noted to confer a 50 percent increased risk for colorectal cancer. The Healthy People target offers the challenge to reduce the obesity of white men to 15 percent of the population by 2010, essentially halving the projected rate. Screening involves currently established techniques, FOBT, and endoscopy (either sigmoidoscopy or colonoscopy). The use of endoscopy, based on a National Health Interview Survey, has increased approximately 50 percent in the United States; this might be maintained or increase to 52 percent (Healthy People estimate), although the optimistic rate projects rates up to 70 percent for screening, similar to mammography. Finally, treatment includes Stage III adjuvant chemotherapy or Stage IV chemotherapy. A decline in mortality has been achieved by chemotherapy.

Dr. Zauber described several scenarios for changes "upstream" and how those might affect the changes "downstream." At the conservative level, the "upstream" factors remain frozen at the levels achieved in 2005. "Continued trends" are a continuation of past trends; if smoking decreases, for example, the mortality rate will continue to go down. In addition to Healthy People 2010 specific goals for upstream interventions, there is an "optimistic" category, which represents a difficult but feasible best case for the levels of upstream factors. Although none of these upstream interventions will achieve the downstream colorectal cancer mortality reduction of 38 percent for white men of the Healthy People 2010 goal by 2010, significant reduction in colorectal cancer mortality can be obtained with currently available interventions.

Dr. Zauber also shared projections of colorectal cancer mortality for 2010, 2015, and 2020 assuming that the best cancer control opportunities are realized. The reduction in mortality was assessed in relationship to past delivery (pre 2005) of interventions, the future delivery of interventions (2005 and onwards), and the remaining reduction to be achieved by discovery and delivery of new interventions. The potential mortality impact of meeting optimistic goals for delivery of screening, treatment, and prevention by 2015 is estimated as 19 percent reduction based on past delivery of interventions, an additional 15 percent reduction in mortality with the future delivery of interventions and with 66 percent reduction remaining to be addressed by future discovery and development. In 2020, the past delivery is projected to provide 21 percent reduction; the future delivery, 21 percent reduction; and the discovery and development, 58 percent mortality reduction. Treatment definitely has an effect; screening, however, has the largest potential effect to reduce mortality rates due to colorectal cancer. Risk factor modification will have a long-term significant effect but only modest short-term effects. Dr. Zauber also presented graphs illustrating "optimistic" results by gender and race and showed that racial disparity is projected to continue even though the currently available interventions will provide marked decreases in colorectal cancer mortality for minorities.

The recently published *JNCI Monograph: Methods for Measuring Cancer Disparities* describes methods for measuring cancer disparities. The CISNET colorectal group currently is weighing various methods offered in this monograph to discern the best interventions with respect to racial disparities in reducing colorectal cancer mortality.

A Web site focused on cancer mortality projections is under development. It will be available publicly and will offer the MISCAN model and model developed by the Harvard School of Public Health. This can be used by health policy analysts, advisory boards, researchers, and others to examine impacts and employ models to inform health policy.

Scientific Opportunities and Policy Implications—Dr. Jon Kerner

Dr. Kerner observed that the CISNET program offers a good model on how to integrate policy decision options with what scientists have learned from research through mathematical modeling of the impact on population health. It presents an example of the investment, which Dr. Niederhuber described this morning, that the NCI plans to make across the institute in computational biology and biostatistics. As Dr. Feuer mentioned, multiple models that can be compared with each other allow one to work through various assumptions and understand a disease control alternatives better. The attempt to factor so many different variables into these models—biological, epidemiological, behavioral, clinical research, health services research, and policy research—provides an example of how the NCI is working to build bridges from cells to society in its activities.

Dr. Kerner mentioned that he currently serves as NCI's representative to the Healthy People 2010 Cancer Chapter. The Office of the Secretary, DHHS, along with the Office of Disease Prevention and Health Promotion, is interested in how this modeling effort could be used to greater efficacy for Healthy People 2020. In addition, the CISNET group recently met with Dr. Jerry Yates from the American Cancer Society (ACS) to discuss collaboration, particularly with these modeling resources, to help the ACS consider its goals for 2015.

The kinds of activities and the accessible Web site that Dr. Zauber described further point to NCI's commitment to translating what has been learned from science into practice. Dr. Zauber mentioned cost effectiveness, and Dr. Berry discussed individualized tailored therapies, both of which suggest that science actually can influence policy decisionmaking, an attractive idea as much policymaking appears to be influenced by many things other than science. As another example of how CISNET can assist, the State of Maryland made a decision several years ago to invest its tobacco settlement money in colorectal cancer screening, and now, because of CISNET's help, has a model to assess the state's investment to achieve its screening goals.

Questions and Answers

Dr. Runowicz asked about the effect of hormonal therapy and risk factors as addressed by the breast and colorectal modeling systems, with consideration given to the work performed by the Women's Health Initiative (WHI). Dr. Berry noted that CISNET models will be used to examine the impact of hormonal therapy on mortality due to cancer, particularly in light of results from the WHI's study, published in July 2002. Dr. Zauber confirmed that hormonal replacement therapy is associated with a decreased risk for colorectal cancer; in future analyses, the model will be adjusted to assume that the prevalence of HRT use will be lower. Dr. Kerner added that the risk factor issues in colorectal cancer tend to have a long-term effect; CISNET offers the feature of comparison to help evaluate the relative impact of different investment options.

Dr. Ralph Freedman wondered about the effect of the adequacy of the screening effect with an annual versus less frequent mammography. Dr. Berry responded that the actual use of screening within the population is modeled and then assessed to determine what would have happened had there been no screening. Dr. Feuer noted that one of the primary data sources used was the Breast Cancer Surveillance Consortium, which tracks a registry of mammography facilities as well as actual population-level data. Dr. Zauber clarified that her examples used data from the U.S. population in the past; in some instances, only 70 percent of the colonoscopies were reaching the cecum, which clearly is not optimal in terms of colonoscopy care.

Dr. Kenneth Cowan, Director, University of Nebraska Medical Center, observed that one of the interesting things about CISNET is that the group is learning to create more effective models. Dr. Kerner

pointed out that approximately one-half of the entries on the CISNET's publications list address this issue. Dr. Cowan suggested that CISNET's greatest impact could be on defining the standards and convincing policymakers to embrace it in health policy decisions; if modelers can help convince policymakers that they can impact the survival rates for cancer, then it could help in terms of reimbursement, coverage, and other issues. Dr. Kerner agreed that modelers will help to shape and answer the questions. He echoed Dr. Niederhuber's thought from the morning session that the hidden issue is accessibility to new technology and added that CISNET provides a tool to understand how best to facilitate this access. Dr. Berry commented that modelers improve their own models by learning from other researchers' models. Dr. Zauber mentioned that models can vary in their "dwell time;" for example, the MISCAN model has a shorter dwell time than the Harvard model, which carries implications for screening.

XII. STATUS REPORT: TRANSLATIONAL RESEARCH WORKING GROUP— DRS. ERNEST T. HAWK, LYNN MATRISIAN, AND WILLIAM O. NELSON

Dr. Ernest T. Hawk, Director, Office of Centers, Training and Resources, provided an interim update on the working of the Translational Research Working Group (TRWG) during the past 6 months. He co-presented with TRWG co-chairs, Drs. Lynn Matrisian, Vanderbilt University, and William O. Nelson, Johns Hopkins University. Dr. Hawk began with the NIH mission statement—"Science in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend health life and reduce the burdens of illness and disability"—which espouses: (1) the pursuit of knowledge, and (2) the importance of applying that knowledge to benefit human risk for as well as living with various diseases. The TRWG's activities remain centered on the latter; the TRWG recognizes, however, that translational research is best when it leads to applications that are meaningful as well as to new knowledge—that is, an iterative process of discovery and application. The NIH mission emphasizes the domains of prevention, prediction, and personalization, and that the future is fueled by translational research. There are many different NCI programs, both investigator-initiated and facilitated, that have activity in translational research. The rationale for change involves three points: (1) advances in cancer biology offer enormous opportunities to improve treatment and prevention; (2) the translation of these concepts into meaningful drugs, devices, and interventions that can be tested in the clinical population has not kept pace with advances in fundamental research; and (3) both the expanding opportunities and the high expectations, together with the current environment of limited resources, require a translational research system to identify and pursue the most promising opportunities efficiently and productively. The TRWG's charge was to evaluate the current status of NCI's investment in translational research and envision its future in an inclusive, representative, and transparent manner. Dr. Hawk explained that the remainder of the presentation would cover the focus of the TRWG's work, activities to date, and its future plans. In addition, Phase I draft recommendations will be reviewed.

One of the strengths of the TRWG is the number of people involved. The committee is comprised of 63 members, and each is an accomplished investigator and in many cases clinician or basic scientist. Most are major leaders in the area of cancer research or care or basic science. They bring unique strengths that together make the whole greater than the sum of its parts. Individuals were drawn from cancer centers, industry, dedicated programs such as the Early Detection Research Network or the SPORE program, individual investigator-initiated program projects, P01s, clinical study consortia, R01s, the domain of training and education, and the Federal Government. There also is a representative from the most relevant Divisions of the NCI. Moreover, from a perspective of patient populations, the membership roster is organized around organ systems, representing 14 major areas of oncology care and research, such as breast, colorectum, lung, prostate, and stomach. In terms of special scientific areas, the TRWG includes experts in prevention, pediatrics, genetics, and drug/immunology, among others.

The TRWG has made a great deal of progress since its formation in late 2005. Accomplishments include: the recruitment of TRWG leadership and members; the review of foundational documents, such as the President's Cancer Panel reports and information about the FDA's Critical Path Initiative; the analysis of the CTWG for ideas, challenges, and lessons learned; the development of a Web-based communication platform and the compilation of public comments on key questions; portfolio and process analyses of NCI's current investments in translational research; the mapping of five developmental pathways to clinical goals; and the establishment of four Phase I subcommittees addressing organization and funding, core services, scientific prioritization, and project management. The subcommittees met through multiple conference calls, and three plenary meetings of the full TRWG were convened. In addition, a public roundtable was held to involve the community, and an industry/foundation roundtable focused on issues surrounding resources, collaboration, developmental pathways, and management. Finally, the TRWG produced draft Phase I recommendations.

There have been five notable products to date. (1) The TRWG prepared a definition of translational research: "Research that transforms scientific discoveries arising in the laboratory, clinic, or population into new clinical tools and applications that reduce cancer incidence, morbidity, and mortality." (2) The focus of the TRWG is on "early translation" as defined in the recent President's Cancer Panel report, (i.e., which deals with partnerships and collaboration, intervention development, Phase I/II trials, etc.), and five developmental pathways to clinical goals to help with early translation were identified and elaborated: agent, immune response modifier, interventive device, risk assessment device, and lifestyle alteration. These are important to bring the TRWG's efforts together to understand what resources are needed, who is needed to do this, what types of relationships and what sorts of activities are needed to realize translational progress. (3) A portfolio analysis reviewed NCI's current translational research activities. The effort relied on established mechanisms in the Office of Science Planning and Assessment and resulted in an approximately 240-page document. Key findings included that awards, the majority of which are given to NCI-designated cancer centers, were not categorized adequately for translational content to provide meaningful quantitative assessment, and that translational research is funded by most NCI Divisions, Offices, and Centers through collaborative, facilitated, and individual mechanisms. (4) A process analysis helped determine how specific translational advances were made. This activity, which involved case studies of 20 examples of translation in practice, revealed that translation currently occurs by a variety of different mechanisms, such as single facilitated programs (EDRN and the SPORE program), a series of individual investigator awards, and the intramural program with some collaboration with other institutes. Moreover, it became clear that diverse stakeholders are required. (5) The TRWG drafted Phase I recommendations, described below.

The broad-scale challenges faced by the TRWG include how to ensure that the most promising concepts enter a development pathway, that those concepts once entered actually advance to the clinic or to what might be called "productive failure," and that the progress along those paths is as rapid, efficient, and effective as possible. The roundtable discussions generated more than 300 specific obstacles and recommendations. Dr. Hawk presented a distillation of seven key obstacles that stand in the way of translational progress. (1) Insufficient coordination and integration across the NCI results in a fragmented translational research effort that risks duplication and may miss important opportunities. (2) The absence of clearly designated funding and adequate incentives for researchers threatens the perceived importance of translational research within the NCI enterprise. (3) The absence of a structured, consistent review and prioritization process across this enterprise that is tailored to the characteristics and goals of translational research makes it difficult to direct resources to critical needs and opportunities. (4) Translational research core services are often duplicative and inconsistently standardized with capacity poorly matched to need. (5) The multidisciplinary nature of translational research and the need to integrate sequential steps in complex developmental pathways warrants dedicated project management system resources. (6) Insufficient collaboration and communication between basic and clinical scientists, as well as the paucity

of effective training opportunities in this area, limits the supply of experienced translational research scientists. (7) Inadequate collaboration with industry can delay appropriate developmental hand offs. These obstacles were considered by the four standing subcommittees that focus on organization and funding issues, core services and coordination issues, scientific prioritization, and project management.

Eight Phase I recommendations were drafted to address these obstacles to translational research. Each subcommittee defined specific goals of the draft recommendations and discussed implementation concepts. At this point, there is a reasonable level of concurrence on the goals of the recommendations and the recommendations themselves, but additional work is needed to further define and agree upon specific implementation ideas. These are presented below.

(1) Flexible organizational approach recommendation: Establish a flexible and integrated organizational approach that will coordinate translational research opportunities. The goals were to enhance portfolio management and coordination, identify and advance the most promising opportunities, reduce fragmentation and redundancy, accelerate progress by ensuring that resources are adequately focused, coordinate the setting of translational research goals, and ensure a dynamic balance of investigator-initiated and prioritized projects. Implementation concepts under discussion include a matrix organizational structure integrating all NCI programs and mechanisms that support translational research and leadership for translational research with authority over the matrix structure. An external advisory committee to advise the NCI Director on translational conduct, oversight, prioritization, and funding has been suggested, with a defined role for the advisory committee and matrix structure in the prioritization process. Another idea put forth was to define the nature and scope of coordination of investigator-initiated projects.

(2) Designated funding recommendation: Designate a specific portion of the NCI budget for early translational research. The goals are to recognize the importance of translational research, manage it as an enterprise, and demonstrate an enduring commitment of the NCI to translational research. The implementation concepts that are under discussion involve the nature and the scope of the translational activities that would be covered by this designated funding, the percentage of the NCI budget that should be designated to translational research, and how best to achieve and maintain a balance between the funds for investigator-initiated projects and major projects that are prioritized through a more comprehensive and system-wide process. In addition, the nature of a coordinated budget management process for these specific activities was considered.

(3) Distinctive prioritization process recommendation: Establish a distinctive prioritization process for early translational research to prioritize goals and to select specific projects to realize these goals. This recommendation aims to identify emerging concepts and translational opportunities that warrant a prioritized effort and to focus sufficient resources on those high-priority projects to ensure that they are advanced efficiently and rapidly through the pathways to the clinic. A third goal is to prioritize the projects through a dynamic, systematic, and iterative process that involves all key stakeholders. The implementation concepts that are under discussion for this particular subcommittee include a Translational Research Prioritization Committee that would act as an external advisory board. Its membership should encompass all key stakeholders and be term-limited to promote dynamism and adaptability. A transparent decision-making process that would draw on broad community input should be adopted. The subcommittee structure should address varied translational research vantage points, such as organs, mechanisms, clinical products, populations, and developmental pathways. Moreover, candidate project concepts should be proposed by investigators, NCI staff, and industry. A final concept is that criteria for prioritization should include scientific quality/validity, technical feasibility, and clinical need.

(4) Tailored funding/review mechanisms recommendation: Tailor funding and review mechanisms for early translational research projects to facilitate and create incentives for researcher participation. The goals of this recommendation were to provide investigators with incentives for risk taking and to reward "productive failure" as well as successful completion. The recommendation also aims to provide avenues for flexibly forming dynamic multidisciplinary research teams and collaborators, reduce the structural lag time between the phases of the research process, and ensure that translational research applications are treated appropriately in review and measured against the appropriate quality measures and objectives. The implementation concepts that are being considered fall under the categories of funding mechanisms and reviews. The funding strategies should reward goal-oriented, large-scale, flexible research teams with awards that create incentives to foster collaboration within and among networked institutions. Another notion is that translational research contains inherent milestones, which could be employed as metrics for bench-marking translational research to reward successful completion or "productive failure." In addition, translational research R01s should include both discovery and translational components. In the review domain, the thought was that translational research projects could be directed to designated study sections or review groups, potentially based on the developmental pathways to clinical goals that were discussed earlier. Furthermore, the review criteria and processes would be tailored to these translational research objectives and often milestone related and would reward collaborations, such as public-private partnerships or other co-funding from industry. A "rolling tenure" review model could be based on a 3+3 year approach, with productive change supported.

(5) Core services coordination recommendation: Establish a system to coordinate core and shared resources and other infrastructure components essential for early translational research. Objectives include facilitating and accelerating access to a broad range of core services, increasing standardization, quality assurance, and cross-core reliability of biomarkers, minimizing redundancy and ensuring efficiency and economy of scale by operating these services at optimal capacity, and making certain that these core services are available in a coordinated and cooperative manner across all funding mechanisms. Ideas for implementation include: an inventory of existing cores to identify excess capacity and redundancy, a publicly accessible information system to track these core facilities, incentive structures that reward consolidation and eliminate unnecessary duplication, and core services that would benefit from regionalization through the creation of centers or networks. Other concepts discussed involved an oversight and certification system to ensure standardization and quality assurance, mechanisms to ensure that the core services are multi-user, service-based entities, and approaches to enhance good manufacturing practices/good laboratory practices (GMP/GLP) manufacturing capabilities.

(6) Project management recommendation: Establish a formal management structure for early translational research. This recommendation aims to speed the translational research process; facilitate recognition of and access to internal and external resources; promote coordination and communication between the project scientific leads and the multidisciplinary project team; facilitate progress across stages, disciplines, and programs; and ensure progress—that is, continued success or "productive failure"—through a periodic review of project milestones. For implementation, it should be determined where the project managers should be located (at the NCI, academic institutions, or both), as well as whether to use individual project managers or a project management team with complementary areas of expertise. The degree and scope of project management for investigator-initiated projects should be discussed. Finally, the roles of the project management system during proposal development and for designated projects need to be considered. Dialogue about this latter aspect should cover coordination with principal investigators to ensure seamless development progress: identifying, facilitating, and coordinating access to resources and collaborators; coordinating regulatory filings and interactions with industry; and monitoring progress based on milestones, including providing input into decisions.

(7) Analysis recommendation: Develop coding and tracking system that allows real-time analysis of the nature and scope of the NCI's early translational enterprise. There is a compelling need for better understanding the NCI's current investments and capabilities. Each of the TRWG's draft recommendations require the NCI to have a more complete, facile, and timely understanding of its investments in translational research. This recommendation specifically addresses this foundational need.

(8) Evaluation recommendation: As the proposed changes in the NCI's early translational research enterprise are implemented, establish a formal evaluation system to assess their impact. To achieve this, a baseline assessment is needed to ascertain NCI's current processes and investments in translational research; this would then serve as a benchmark for comparison following implementation of the recommendations.

The TRWG will continue the Phase I subcommittee work and constitute Phase II subcommittees to develop draft recommendations on two new topics: external integration and workforce/training. It will present another interim report to the NCAB in September 2006. Regarding the draft Phase I recommendations, public comment will be solicited via NCI's Web Site in fall 2006. A second public roundtable will be convened at that time as well to discuss Phase I and II draft recommendations and solicit ideas regarding implementation. Implementation plans will be developed, and the final model, recommendations, and implementation plan will be presented to the NCAB in winter 2007.

Questions and Answers

Drs. Runowicz and Hawk discussed the TRWG's focus and activities in light of the Clinical and Translational Science Awards (CTSA) initiative that Dr. Zerhouni referenced in his morning presentation. Along with Dr. Linda Weiss of the NCI Cancer Centers Branch, Dr. Hawk serves as one of the NCI's representatives to the CTSA. The CTSA process was patterned after the NCI Cancer Centers, including guidelines that were broadened to transcend an individual disease; moreover, the CTSA intends to facilitate translational and clinical sciences. Dr. Hawk stated that there is no attempt to duplicate efforts, but the themes are similar because productive translational science requires those types of activities.

Dr. Niederhuber commended the three TRWG co-chairs on a remarkable job in dealing with one of the more difficult assignments that the NCI has put forth, especially in accomplishing the inclusiveness of the community at large. He added that the TRWG is building on the work of the CTWG, and rather than duplicating the NIH's activities, the NCI will probably lead the process of how one does translation and how one does clinical research in the area of early phase drug discovery with the help of these two working groups. Dr. deKernion requested clarification about the structure of the large TRWG enterprise. Dr. Nelson responded that Dr. Matrisian's earlier description was apt and agreed with Dr. Hawk's point that labeling the translational components of NCI's portfolio was a difficult task.

Dr. deKernion requested further details on tailored funding review mechanisms. Dr. Hawk said that this is an issue to be addressed; although the NCI has mechanisms that are doing a fine job of translational research in their own realms, there are several groups all working somewhat differently in the same domain. He pointed out that it is not clear that everyone is applying the term in the same way. The TRWG sees a need for communication, collaboration, and coordination among existing mechanisms rather than starting everything over. Dr. Nelson pointed out that flexibility was built into the SPORE mechanism to discontinue a project in favor of another one; it was hoped that a discontinued project was a result of a productive failure and that milestones achieved would be counted as a success.

Next, Dr. deKernion expressed the view that there is duplication and multiplication among core mechanisms and a greater efficiency could be achieved. Dr. Hawk commented that the TRWG process

has witnessed the initiation of self-appraisals by several existing translational research programs. For example, the SPORE program is re-examining itself and refocusing its effort to work more productively in the future. Cancer centers are accomplishing this partly through self-assembly. Many people are telling the NCI that a re-consideration of cores or shared resources is an important area to invest in just as the P30/P50 commission did a few years ago. That said, redirecting some of the NCI's energies and resources to more productive uses will take a lot of work and commitment—by the whole field working in concert—if it is to be as productive as possible. Dr. Nelson recalled that the P30/P50 subcommittee had a consistent mandate to tackle this problem, and asked Dr. Cowan, who had chaired that subcommittee, to share his thoughts. Dr. Cowan congratulated the TRWG co-chairs on the progress made to date and observed that, rather than duplicating the CTSA, the NCI and cancer research should be able to leverage the investment of the NIH into the CTSA as another way to incur efficiencies in the core facilities. There have been far more productive failures and a limited number of notable successes, and the NCI needs to understand whether those productive failures were really productive failures because they were not really ready for prime time or whether barriers existed that prevented success. The TRWG mechanism could help work through such barriers and turn some of those productive failures more into successes. The coordination and facilitation will continue to be complex and challenging, but this group is well prepared to deal with it.

Ms. Giusti asked whether the TRWG will provide recommendations on how the NCI's translational research portfolio might change in terms of allocations to different programs that contribute to translational research, and what specifically would represent a success of the TRWG's efforts following implementation of its recommendations, perhaps 12 months from now. Dr. Hawk responded that the second recommendation, which suggests that NCI should make a specific commitment to translational research has significant support within the TRWG, but exactly what that commitment should look like in terms of dollars, programs, or partnerships ultimately may be decided by the NCI and its advisory boards, rather than by the TRWG alone. With regard to the question of a key success of the TRWG, Dr. Hawk noted that few if any tools existed within the NCI to help inventory the translational research activities when the TRWG embarked on this mission. The compilation of the data on translational research within NCI is a success in and of itself. In addition, Dr. Hawk commented that each of the eight draft recommendations is important. In terms of cost savings, Dr. Hawk thought that the core coordination will be critical; many TRWG members commented on the need to find opportunities to work better and more efficiently. Dr. Matrisian added that having the metrics to know what does or does not work is valuable. Dr. Nelson said that he has acquired a lot of optimism during this process, noting that industry participants and various stakeholders in the community have told the TRWG that it is tackling the right problems. Implementing any of the recommendations will leave the industry immeasurably better off.

Dr. Barker complimented Dr. Hawk and his colleagues on organizing the TRWG and understanding the state of translational research in the NCI. She pointed out that, whatever is structured or accomplished by the TRWG, it actually is engineering a culture shift; this is a topic that has been discussed throughout today's meeting. She also noted that there are organizations, such as the Department of Energy, that have done this and have matrix models in scientific environments that work pretty well. The NCI can learn from these entities. She suggested that Dr. Hawk is proposing a hybrid of one of those organizations, a type of drug-development, project-leader enterprise.

XIII. UPDATE: INTEGRATIVE CANCER BIOLOGY PROGRAM—DR. DINAH SINGER

Dr. Dinah Singer, Director, Division of Cancer Biology, provided information on the background of the Integrative Cancer Biology Program (ICBP). She noted that Dr. Niederhuber had identified computational biology as a major area of interest for the NCI. The ICBP program is the vanguard of that

effort to bring some of these approaches to cancer biology with extensions to the other areas of the NCI. It began with the recognition that there is still much more to understand about cancer, although much has been learned during the past 10 years. Cancer now is recognized as primarily a disease of genes, and much is known about those genes: their regulation, interaction, what their products do, signal transduction pathways, mechanisms, and metabolic pathways. This reductionist approach has been informative and has highlighted the complexity of the cell, both the normal and the cancer cell; yet, despite all of this information, scientists still cannot put it together to form a cohesive picture. The ability to address the complexity of the cell and of cancer has been limited by large datasets that can be analyzed linked to an absence of the appropriate mathematical and computational approaches to generate scaleable, multivariate models that are dynamic and, most importantly, predictive that can be the basis for experimental design. As the ICBP was being developed, those limitations were being addressed. There were an increasing number of large datasets being generated that described various aspects of cell biology. At the same time, computer-based modeling was being developed, particularly in mechanical and electrical engineering, to model and analyze a variety of complex systems. The ICBP brings those two areas together to integrate what is known about cancer from the reductionist approach and apply the new mathematical models, modeling abilities, capabilities to the biological systems, and the increasing number of data sets.

The short-term goals of the program are to: facilitate the development of models and computational modeling; link it to further work and experimentation in cancer biology; and develop the appropriate models for molecular dynamics, cellular interactions, and organ and tissue interactions. The long-term goal is to facilitate the development of the whole field of integrated cancer biology. That will bring together in an ongoing productive way cancer biologists, mathematicians, physicists, engineers, and programs such as the nanotechnology effort and the CISNET, for a large-scale effort. Training is a critical part of this to educate people in a common language and a common approach. The ICBP has been in existence now for about 1.5 years. Dr. Singer introduced Dr. Daniel Gallahan, Program Director, ICBP, to describe the program's structure and progress to date.

Overview—Dr. Daniel Gallahan

Dr. Gallahan expressed his appreciation to the NCAB for the opportunity to provide an update on the NCI's Integrative Cancer Biology or Systems Biology program. He observed that much of the day's discussions have pointed to the need for this type of program, both in the comments that were made in the morning by Drs. Niederhuber and Zerhouni in terms of the complexity of disease, as well as the CISNET program and finally in Dr. Hawk's presentation about translational aspects; one of his slides had included the ICBP.

The ICBP was instigated out of the need to develop an integrative or systems approach to the understanding of cancer. Dr. Gallahan displayed a graphic that showed its approach involving systems biology and computational modeling. The systems biology deals with the networks of the genes and the ongoing processes and cellular interactions. The computational or modeling approach is brought about through the mathematical processes and different computational tools to make predictive models that can describe certain processes within the cancer cell and the cancer process. In actuality, these are integrated together and form almost iterative processes where one defines the other in terms of the integration. The ICBP takes this vast amount of clinical, biological, and epidemiological information to understand and generate new discoveries and knowledge, and ask questions that have not been posed through the classical reductionist approach. The aim is to have both basic and translational impacts on this. An extensive educational outreach program is another critical component of the ICBP. The NCI realized, with guidance from the NCAB and the BSA, that it was necessary to leverage as much as possible

extensive education and outreach not only for the investigators but also for the public and for those that it would be impacting.

The expectations are that the ICBP will: (1) develop and implement integrative cancer biology within and among the centers, and even leverage beyond the individual centers themselves; (2) create an organizational and scientific focus for the broader integrative cancer biology community; (3) serve a leadership role for this research community, providing advice and guidance to the NCI on gaps and opportunities in developing the field; and (4) establish educational and outreach programs.

The ICBP has funded nine centers, three of which are planning centers. The centers work across the spectrum of cancer biology dealing at the genetics and epigenetics level all the way up through signal transduction and sophisticated three-dimensional modeling of tumor progression. All of these centers characteristically have associated the three components of the systems biology approach, computational modeling, and education and outreach.

The current ICBP activities include: the development of validated siRNA library of cancer genes; the molecular characterization of a set of cells from the Sanger Institute (800 cell line set) that have been characterized by sequencing; a summer training program in integrative cancer biology where each center has adopted an undergraduate student to work in the laboratory with various mentors; the pilot of a "digital Model" repository; and an interdisciplinary team building and interaction.

ICBP Modeling Processes—Dr. Douglas Lauffenburger

Dr. Douglas Lauffenburger, Director, Division of Biological Engineering, MIT, described the work of one of the nine ICBP centers, in which he is co-principal investigator, along with Dr. Richard Hynes. Some of the scientific questions that the ICBP is addressing through the center includes the origin and repair of mutations in DNA, understanding of a network that is highly dysregulated in a wide variety of cancers, understanding of a particular cell function that is crucial in progression, and some of the core efforts in generating methodologies. Moreover, the work being performed is quite interdisciplinary. Dr. Hynes is a well-known cell biologist, and Dr. Lauffenburger is a biological engineer; their team consists of people from biological sciences and engineering, and each of the project areas is being addressed by teams of graduate students, postdoctoral researchers, and faculty who come from different disciplinary backgrounds.

The aim is to understand what properties of the components of a system—in this case, a phenotype—affect its behavior or operation. The phenotype might be at the cellular, migration, proliferation, death, differentiation, or tissue levels; Drs. Hynes' and Lauffenburger's team focuses on the molecular level states and activities, seeking a predictive understanding for how the system phenotype changes when any of the molecular component properties are changed. This could be considered in terms of either biomarkers or targets. Many types of models can be created for those purposes, depending on what is known or being answered, in terms of the components and mechanisms. Models that have to do with cause and effect can be constructed in a logical way, as well. Dr. Lauffenburger presented two examples: one that lives in the realm of mechanism, and one that lives in the realm of cause and effect logic and influence. He pointed out that, along with the different types of computational methods, the system can be analyzed and predictions made regarding what will happen at different levels of the biology. For instance, in a process dealing with migration, invasion, and metastases, models may be needed for the actual biophysics of how cells migrate through tissue or how biochemical signals regulate the biophysical processes. The reason for needing this whole modeling change is because different types of therapeutics or drugs act at different stages. Avastin®, for example, would interrupt the actual generation of signals at the stimuli level, whereas Gleevec® would interrupt at the intracellular network of

the signals being generated, and Velcade operates mainly in terms of the biophysics of how the cellular function is carried out.

Dr. Lauffenburger focused on the process of cell migration, which is important both on the tumor side of the question in terms of tissue invasion and metastases and on the host side of the equation in terms of angiogenesis and vascularization of the tumor. His center's main study has been on the invasion of primary tumor cells. Cell migration involves a complex process of extending membrane and forming adhesions with its environmental matrix, generating force that pulls it along, detaching it from the rear. To understand how migration works, models need to be developed to show how all these biophysical processes work together. The biophysical processes are regulated by cues in the environment such as hormones, cytokines, growth factors, and extracellular matrix. They generate intracellular signals, which need to be modeled. These projects are an intimate coupling between experiments and models.

Dr. Lauffenburger shared data from a study and posed the question about what mechanism in a cell's biophysics enables it to be highly invasive in one tissue, but not in another tissue, regardless of the cell's own genetic makeup. There are some regimes in which the ability of the tumor to crawl through a tissue is totally inhibited and would stop that invasion, but in other tissues it would be highly invasive and the therapeutic would actually make matters worse and perhaps affect metastasis. He noted that all of the mechanisms involved in protruding membrane, forming adhesions, contractile force, and detachment play a role. The experimental measurement of how fast the cells are crawling serves a function of what researchers do to the matrix in terms of the matrix components.

Drs. Hynes' and Lauffenburger's team created a biophysical model in which all of these processes that have been worked out in terms of membrane protrusion and forming adhesions, between adhesion receptors and matrix, and metalloprotease, degradation of the matrix, and generation of contractile force and de-adhesion, and can be put together computationally. Based on this, another model can create *a priori* predictions of different properties of a cell receptor level or extracellular matrix adhesion sites or stiffness or core size, and predict the invasiveness of a cell.

The team also has completed some work regarding controlling biophysics in terms of creating models about signalling pathways, using the same kind of data on how fast cells migrate under different conditions of matrix and stimulation. The issue at hand was whether, using about one-half dozen protein signalling activities, a model could be created to determine whether a specific cell was invading a tissue, and which pathway(s) would be targeted to effect intervention. Dr. Lauffenburger reported success in employing a cause-and-effect model. Experiments are underway with inhibitors for some pathways to predict which inhibitors will drive cells to lower or higher motility under differing conditions.

Dr. Lauffenburger concluded by noting that the thinking processes and computational capabilities are now in place, and what is needed is to increase high-throughput protein level measurements, whether by flow cytometry, mass spectrometry, protein microarrays, live cell imaging, or high-throughput protein kinase activity arrays. These kinds of measurements will allow researchers to move these models from one-half dozen pathways to a much greater comprehensive coverage.

Cancer as Information—Dr. Todd Golub

Dr. Todd Golub, Dana-Farber Cancer Institute, explained that there are clinical states (e.g., cancer states of various aggressivity or drug sensitivity or resistance) and biological pathways that are important in various types of cancer. It is challenging to integrate these types of information in a way that is useful. Dr. Golub approached this by asking whether one could describe these clinical states and these biological states in a common language, which he proposed as the genome. He presented data that referred

primarily to RNA gene expression levels that, for example, could be used with proteomic data; in short, it collapses and integrates multiple systems (e.g., biological or experimental) and clinical observations into a common parlance. Computational methods then can be employed to define a signature, such as a genomic signature, that is reflective of the state of a clinical or biological pathway of interest. Dr. Golub noted that a gene expression profile is not a new idea and provided an example of using gene expression signatures to define cancer subtypes based on a molecular taxonomy that are moving into the arena of diagnostic testing. Predicting metastatic potential in breast cancer is the most famous example, as the test is available commercially. This approach could be used in experimental systems to identify the signature of genes that one might then follow up each gene one at a time in terms of its functional importance in that biological process or clinical process. Dr. Golub stated that the question being asked is whether one can use these signatures of, and the information correlated with, the biological states to help modulate those states toward therapeutic advantage.

One can take a disease process or a signalling pathway of interest, such as a gene expression profile, and cast it in the language of a genomic signature. As these genomic methods start to evolve, the question under consideration is whether one could use the signature itself as the starting point for a high-throughput small molecule screen, which could then be used as a tool to dissect the biology, as well as for future clinical development. Dr. Golub described the situation where there are two biological states of interest in terms of the epidermal growth factor (EGF) receptor. One state could be the EGF receptor activated in the cell in a lung cancer. The other state could be the signature of that lung cancer cell where the EGF receptor has been inactivated. One might query about any small molecules in a library that are able to turn this signature to the state of interest, and by inference, induce the cell to enter the biological state of interest. To screen 10,000 small molecules, which is a modest-sized chemical library, in the usual way would take 10,000 Affymetrix arrays at a cost of about $5 million. A method that measures only the signature of interest, not the entire genome, is about 1,000-fold cheaper; at approximately 50 cents per sample or per chemical in a small molecule library, one can measure the signature of interest and examine whether something will trigger the signature of interest, and by inference, trigger the biological state change. Dr. Golub showed the proof-of-concept experiment, which defined the signature of acute myeloid leukemia and the signature of normal mature blood cells to determine if any small molecules in a library would induce this normal signature in a leukemia cell line. He reported that a class of proteins (a class of inhibitors, small molecules, and some of them drugs) were shown to induce the maturation of acute myeloid leukemia cells, and this discovery was found entirely on the basis of a signature. No one had thought that these molecules might play a role. Dr. Golub pointed out that: (1) a clinical trial is beginning in Boston to test Iressa at the maximally tolerated dose in patients with relapsed or refractory acute myelogenous leukemia (AML), and (2) this result was an unanticipated and previously unknown activity of these drugs. He suggested that a recurring finding will be that existing FDA-approved drugs, or drugs in clinical development, have many activities, and that systematic tools will be needed to be able to identify those so-called off-target effects. The signature approach could be employed in such a way.

Dr. Golub next shared a study of prostate cancer, where the goal was to determine the importance and involvement of the androgen receptor in prostate cancer, specifically the process by which androgen and testosterone binds to its receptor, moves to the nucleus, and brings together other co-activating proteins to turn on genes that are important for prostate cancer survival. This is a complex process that has been worked out in basic biological detail and yet essentially all of the effort to pharmacologically modulate this androgen receptor pathway is targeted at blocking—for example, testosterone from binding to the receptor or inhibiting the body's production of testosterone. The study screened a number of small molecules to determine whether any small molecules could move the cell into the androgen-deprived state by virtue of recognizing computationally that the cell has acquired this molecular signature of androgen deprivation. The researchers came up with essentially two classes of small molecules; both are natural products that have been around for millennia. Gedunin, for example, which comes from the neem tree,

has been used for several thousand years, particularly in India, but nothing is known about its mechanism of action. Dr. Golub showed how these natural products affect the signature of a prostate cancer cell that was stimulated with androgen or testosterone. When it is stimulated with androgen and increased concentrations of celastrol, a natural product, are added, the signature reverts to the signature of a state of a cell that is as if it is not seeing any androgen stimulation.

A publicly accessible database of molecular signatures, that would work similar to a Google search, would be useful. For example, a scientist has a chemical or a drug that affects cells but does not know what it is or its mechanism of action could plug in a query signature, send that signature to a database, and computationally identify whether any signatures in the database look like it, and thereby infer its mechanism of action. Dr. Golub's team performed this with celastrol and gedunin compounds. The conductivity map revealed their similarity with four drugs. One of these, geldanamycin, was developed at the NCI as a heat shock protein binding inhibitor, variations of which currently are undergoing clinical evaluation. Dr. Golub displayed a picture of its structure, which is different than the structure of celastrol or gedunin compounds, but this information that they have the same consequence on the cell has helped to generate the hypothesis that, in fact, these natural products may be novel hsp90 inhibitors. It is known that the androgen receptor is a cleaved protein of the heat shock protein 90 complex that is required for stabilizing the expression and localization of the androgen receptor. If prostate cancer cells are treated with celastrol, the androgen receptor almost entirely disappears, which explains why the signature goes away.

In conclusion, cancer states can be described in terms of genomic information, and high-throughput chemical screens can be based on such signatures. In addition, a large-scale, public domain database is warranted. Finally, navigating cancer biology will mean navigating genomic information.

Questions and Answers

Dr. Niederhuber requested further details on how this impacts on the rapidity and cost of drug discovery in more detail. Dr. Golub focused on the mining of drugs that already have been clinically developed and have received FDA approval; he said that a systematic way to identify new indications for existing drugs could have a dramatic effect on the case of clinical translation, although it would have less effect on organic compounds that have not endured standard safety testing. Dr. Niederhuber asked how one would construct a readout in a mathematical model or obtain information that would be interpretable and usable. Dr. Golub observed that generating the data would pose a challenge; computationally, however, the methods to extract a pattern would not change much. Dr. Gallahan added that, regarding clinical and mouse proteomics, the NCI will be holding a joint meeting in November 2006, in an attempt to bring this sort of information into these modeling efforts.

Dr. Barker wondered what it would take to build this database that Dr. Golub mentioned, and what the NCI's role would be in facilitating such construction. Dr. Golub recognized that it is a complicated issue and reiterated the need to maintain such a database in the public domain without question and without restriction of how people use the information. He suggested that the method should be as systematic and low cost as possible and to build consensus around how to instantiate this initial database. His team has generated about 500 profiles that represent 150 FDA-approved drugs. There should be public accessibility to profiles of all FDA-approved drugs. Dr. Barker commented that she and Dr. Golub could discuss this further at a later time.

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), 552(b(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 their participation in the deliberation of any matter before the Board to be a real conflict or that it would represent the appearance of a conflict. Members were asked to sign a conflict-of-interest/confidentiality certification to this effect.

The en bloc vote for concurrence with IRG recommendation was affirmed by all serving Board members present. During the closed session of the meeting, a total of 2262 applications were reviewed requesting support of $952,803,513. The subcommittee adjourned at 5:10 p.m.

XVII. 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 138th regular meeting of the NCAB was adjourned at 5:30 p.m. on Wednesday, June 14, 2006.